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The Ways of Doctors and the Practice of Physic

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IN THIS year of grace, one planning to compose an essay finds at his disposal a vast wealth of subjects of transcendent importance, all stemming from possibly the most stupendous exhibition of man's usual unfortunate activities since our first forefathers descended from their arboreal perches. The war in general, postwar America, Europe, Asia, the atomic problem, and, should he desire to be local in his effort, the growing economic strife, socialized medicine, the future trend of education; these and countless other topics offer themselves to his pen. In deference to the intellectual stature of this Society and the dignity of his office, your speaker has surveyed these various themes, seeking for that one which would contribute to the annals of the Society a most noble and everlasting epic. But, as subject after subject was considered, scrutinized, and pondered, it soon became evident that beyond an introductory paragraph or two, nothing further seemed to happen. He possessed just too little accurate knowledge, and pride prevented your essayist from wishing to emulate the Judge in Wolfville Days of whom the old cattleman said, "The colonel is just an ordinary liar and you can listen to him. But the Judge, he is something beyond Nature, for whenever he opens his mouth there is a diminution in the sum total of human knowledge."

So we descend from the clouds, sadly abjure the opportunity to "elegantly eructate our erudition" and present a homely little dissertation upon the ways of doctors, and the practice of physic.

*Presented at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

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Long ago, wise men divided the facility of medicine into three somewhat vague but major components, priestcraft, art, and science, and it is the varying ratio of these three factors in the teaching and understanding of medicine which has produced the type of doctor and of practice during the ages.

With the emergence of man from the Cro Magnon phase, the healing art was controlled by the priests and medicine men almost entirely, and divine aid was the only medication to which they had recourse. Incidentally, should one doubt the efficacy of treatment by suggestion and by the intervention of supernatural factors, one need only to observe the effects a Navahoe "sing."

However, even during this era, an attempt at art appeared because the Shamans and the priests sought to reinforce their appeals to godly therapeutics by prescribing the most nauseous and repellant mixtures to be ingested by their patients while the elaborate ceremonies of the ritual appeal to the gods were going on.

There remain many vestiges of these priestly times in the medicine of today. In many schools, the Hippocratic oath is still solemnly read to a partially awed but mostly cynically amused graduating class. Generally the reader rather diffidently interrupts himself to explain that all of the statements of prechristian credo are not to be understood literally, but that idealistically and historically the oath is of some vague but unquestioned merit.

Then, too, there may be noted the remnants of a sort of phallic worship of the uterus in the veneration of this viscus still entertained by some of our modern gynecologists. To ablate this sacred organ except upon the most drastic indication is to sacrifice it and to commit some sort of offence, though against whom or what does not seem to be disclosed. One may note that other organs of the female cosmos are not at all revered, and the thyroid and gall bladder are eradicated with no compunction whatever. Only the uterus, "the birth mother," is surrounded by these ancient taboos.

The tenacity with which theistic dogmas persist in medical thought is revealed by the insistence of certain sects that the spiritual welfare of their communicants outweighs all bodily disabilities. The refusal to permit the termination of pregnancy, even though the mother is in imminent peril of her life should gestation continue, and the general acquiescence of the profession in this dictum in deference to the will of the spiritual advisor rather than the obvious and real need of the patient is still all too common. Slowly, however, all of these atavisms are fading in the light of reason and scientific thought.

The transition of medicine from the primitive state to its comparatively rapid development as a realistic art coincides with the emergence of the Greeks and the Hellenic mind. These people pursued the study of medicine objectively from the practical side and paid scant attention to philosophical speculation. As Riesman well says that little can be added to the picture of disease left us by the Hippocratic school—their power of description kept pace with their power of observation. This objectivity is pre-eminently a Greek quality and, in addition, they had a generally sane attitude toward Nature; their master minds taught medicine, not magic.

With the conquests of Rome, medicine and, indeed, all things concerning pure art or scientific reasoning suffered a great decadence, and had it not been

for the Arabian School which maintained high standards, the profession might well have been completely degenerated into mere charlatanry. However, even with the curious excrescence of astrology which came to medieval Europe chiefly through the Arabians and the Arabists, it was this group which preserved many of the Greek texts and to whom modern medicine owes so much.

Slowly and painfully (to patient as well as to the toiling student) the art of medicine began to develop in a rational fashion. Indeed, this epoch coincides rather closely with the general rise of rationalism in Europe. The obstetric forceps began to supplant the ingeniously devised syringes for the baptism of the unborn child, the ligature replaced the hot pitch application to control hemorrhage, and the rudiments of pharmacology began to appear. Before too long the art and craftsmanship of the physician had reached a high level, and naturally there arose acrimonious controversies as to the superiority of one method of procedure over another. Some of these disputes gave rise to the most eloquent and satisfying polemics, indeed, many of them would do credit to any ultramodern professional disagreement. Next came the period of instruments of precision, the discovery of bacteria as factors in disease and the development of organic chemistry. These first steps toward the making of medicine an exact science, more or less, have been followed by ever-lengthening strides until one might almost conjecture that, by study with precision methods alone, absolute diagnosis might be attained without the doctor ever having seen the patient, but having simply digested the findings of various investigations.

This scientific age brought with it that curious period of therapeutic nihilism during which the great exponents of medicine expressed no interest whatsoever in the amelioration of the sick persons suffering, sharply decried the administration of drugs to relieve mere symptoms, and insisted upon a complete and perfect diagnosis to be confirmed, if the patient was so obliging, by the results of autopsy.

It was in this period of development that the absurd reverence for the history of the case, the anamnesis, arose. Years ago some snuffy, dry-as-dust German professor enunciated the doctrine that the history of the case was the very keystone of diagnosis, and that this document increased in value in direct ratio to its verbosity. This dictum was eagerly absorbed by the native and foreign students of the period and was soon brought to America where, with our passion for mass production, case histories soon became veritable encyclopedias of misstatement.

The almost sacred process of so-called complete history taking was so impressed upon the student and intern that hospital records especially, in the more highly organized institutions, are often volumes of confused and largely imaginary accounts of the past ills and the genetic misfortunes of over-articulate and under-intelligent persons.

Indeed, even an accurate and correct anamnesis is of very minor importance in the diagnosis and management of disease, but in many schools this whole subject is surrounded by an aroma of sanctity, almost ritual.

While precision methods are steadily being expanded and more and more exact mathematical formulas begin to be employed in evaluating body function

in health and disease, suddenly there appear on the bookshelves and in the medical journals portentous essays upon what is euphonistically entitled psychosomatic medicine, and lo! the wheel has turned full circle and we are back at the beginnings with suggestion and ritual again the dominant forces, and with our ancient priestcraft reappearing in a leading role. With a difference, however, it must be confessed.

During the several ages when medicine was first one thing and then another, the relationship of the doctor to the public and the esteem and respect in which the physician was held fluctuated almost in direct ratio with the realism and search for truth or the mumbo jumbo with which doctors ornamented their profession. Thus, among the Greeks and the Egyptians, the medical man was respected as a scholar and a little feared as possessing perhaps a too intimate acquaintance with the force of black magic.

Later, in the decline of Rome, the physician had sunk to a deplorably low estate, and was in part a sort of servant, in part a healer. From early times, and often during the Middle Ages, medical attendants frequently suffered physical punishment and even death if they failed to cure their patient. It is told that Astragosilde, Queen of France, on her deathbed, begged her husband, Gontrano, to throw her doctor out of the window immediately after her death, which was done with the greatest punctuality (Reisman).

As of this time, conditions among medical men are not quite so perilous, we being merely mulcted of our savings by malpractice suits rather than suffering floggings, flayings alive, or other cheerful diversions of an earlier and more artless epoch. More lately, the doctor has regained his high estate, and is in general regarded as an important and authoritative member of the community.

If one reflects upon the uneven progress of medicine down the years, one is arrested by the manner in which the profession has been engaged continuously and conscientiously in an untiring effort to encompass its own destruction.

That the effort has failed, at least in considerable measure, is due not to any lack of zeal on our part, but to the stubborn refusal of Nature to reveal certain secrets concerning the mechanism of disease and to the inability of fallible human intellects to penetrate the recesses of biology deeply enough to obtain this knowledge.

It would seem no great exaggeration to say that if every research problem now in progress in every laboratory in the world were to be solved suddenly and correctly, that medicine, as we know it, would cease to exist, at least for practical purposes.

When the cause of a disease is understood, prophylaxis against its development becomes automatic, so that it is fair to assume that once complete knowledge is attained the function of the practitioner of medicine will be reduced to the supervision of births, the management of lesions due to trauma, and the amelioration of the distresses attending senescence and decay. To this one might add, and a gleam of hope is offered by the suggestion, that there would remain so many persons either too stupid or too indolent to avail themselves of prophylaxis; this group being of such large proportion (at least in a world where the present system of private medicine prevails) that a considerable

army of doctors would be necessary to minister to their ills. This universal willingness to sacrifice its own rewards and emoluments in the interests of the general health is one of the noble attributes of our profession in which the humblest student may well take pride.

Despite the thousands of keen eyes, sharp ears, and alert minds that have been employed in attending the sick, it is amazing how so many seemingly obvious facts not only of pathology, but of anatomy and physiology, too, managed to escape attention for so long.

In some instances this lag is wholly inexplicable, in some it is due to the authoritative opinion of certain distinguished physicians who have daunted discoveries by devastating discussion, and sometimes by lazy and indifferent observation by those who, like Mark Twain's description of Fenimore Cooper, "deal freely in important omissions."

Among the inexplicable delays is the matter of the fetal heart sounds. The heaving, distended abdomen of the gravid woman has ever been a source of unending interest and speculation to those with whom she is in intimate contact. Husbands, friends and neighbors, midwives, doctors, all love to observe and comment upon this phenomenon, and yet it was not until 1828 that Mayer of Geneva was able to announce the fact that the fetal heart tones not only could be heard through the maternal abdominal wall, but the heart rate might actually be counted.

Assuming that the first pregnant woman became an object of family concern some 50,000 years ago, this item of gestational physiology seems to have been overlooked overlong.

To find a truth and have it repudiated and neglected by the leaders of the profession is one of the bitter things for the discoverer, and often an incalculable calamity for the world. In 1827, Melier, a young intern in a Paris hospital, expressed the belief that inflammation in the right iliac fossa depended upon disease of the vermiform appendix. He reported undoubted cases of appendicitis confirmed by autopsy. He described gangrene, perforation, concretions, and peritonitis. He sought to make it possible to diagnosticate inflammation of the appendix, and believed that if the diagnosis could be made, operation was demanded.

The great Dupuytren arose in discussion and destroyed that young surgeon.

For over half a century the profession followed Dupuytren, who was wrong and rejected Melier, who was right; and scores of thousands died who might have been saved.

The man who had the truth was no more heard of in surgery. His further life history is unknown, and he disappeared into oblivion.

How all too common are such ill-considered acts by men who have attained great eminence but who possess in high degree the ability to draw mathematically precise lines between unwarranted assumptions and foregone conclusions.

The great controversy regarding the infectious nature of puerperal fever belongs in the same category, although here there is also much slovenly thinking; but whether or not the work of Sister Margaret Kenny in the management of poliomyelitis is another example of the same sort, deponent saith not.

These unaccountable lags in observation are mentioned, not in a disparaging sense, but merely to emphasize the remarkable development of medicine as a whole. The advances in our knowledge of biology in its broadest sense are awe-inspiring, and in no other field of human endeavor have investigation, experiment, and logical thinking eventuated in such a vast array of known and proved facts.

Consider now the graduate in medicine as he firmly clutches his diploma, that magic scroll before which the doors of practice open wide, and prepares to return to the renter thereof his hired cap and gown. His mind is an intellectual miscellany of the assorted facts and theories with which it has been crammed for four long years, and he is greatly occupied as to his accumulated knowledge in reducing chaos to mere disorder.

He has been taught a bit of priestcraft, more of the art of medicine, and a vast deal of abstract science, a reasonable amount of which is not at all true. How is it possible, one asks oneself, that a man so prepared can face the grim task of healing the sick which lies before him?

The answer is very simple. The ills to which the flesh is heir cannot be sorted out and catalogued as to which require the purely academic biological approach, which demand art, and which priestcraft; but most diseases are in themselves, a melange of mechanical failures, to be managed by art, errors in metabolism, or body chemistry which fall into the domain of pure science and a vast inchoate mass of psychic maladjustments and mental aberrations which are only amenable to priestcraft in its highest sense.

So that our doctor, himself a compound of these three great facilities, is excellently well equipped to deal with the manifold problems of human illness far better than he could possibly be were the groping ideas of our Aesculapian forefathers to be discarded in medical teaching and replaced by pure experimentally proved facts.

There remains the question as to how well this diverse teaching has been carried out, how well the student has been prepared to absorb the information he receives, as well as how he stands in regard to general culture including familiarity with the humanities without which his horizon is and must inevitably remain, narrow and merely technical.

It is an ill thing to analyze one's fellow craftsmen critically, and surely not a safe or wise method of acquiring merit, yet what has to be said, must be said.

Doctors, as a professional unit, are definitely lacking in general culture. Of course, countless individual physicians have attained pre-eminence in the liberal arts and have made distinct contributions in all of the ramifications of cultural endeavor. However, this is not true of the profession in the mass.

Should a bassoon player in the orchestra unfortunately rupture a blood vessel in the course of his Aolian exertions, it would generally be quite difficult to requisition a physician from the audience to administer first aid, but should the conductor of the symphony engage in fisticuffs with his "concert meister," the stage would instantly be crowded with a whole posse of lawyers eager and prepared to manage the necessary legal procedures. The same con-

dition prevails in most cultural fields, and it is rare that one is beguiled by informed and interesting conversation when in the company of a group of doctors.

How uncommon it is to find members of our profession devoting themselves to great national and world problems (other than those concerned with health) when it would seem that their intimate and personal contacts with so many persons must give them a deep insight into the aspirations and needs of people as a whole.

When a doctor utters such libelous attacks upon his own colleagues he lays himself open to Sidney Smith's description of the bishop. Smith said he could never reconcile himself to a belief in the Apostolic Succession until he met the bishop of Bath and Wells, and found in that individual physical and spiritual attributes so absolutely identical with those possessed by Judas Iscariot that he could no longer doubt the truth of the direct descent, one from the other.

It becomes imperative that one making such sweeping statements as the foregoing should be able to justify, or at least to offer some reasonable and applicable explanation.

To say that a lack of general culture among doctors is due to their inferior intellectual stature is manifestly absurd, since no man not far above the average in mental ability could hope to survive the rigors of a medical education, and one need only point to the power of inductive reasoning which characterize scientific research and the solution of the confusing and intricate problems which fall to the doctor to prove conclusively that the physician's mind is in general far above the average.

It has been suggested that the exigencies and fatigues attendant upon the practice of medicine leave no time for cultural activities, but this does not seem to hold true, because taken by and large, doctors do have leisure, at least for golf and bridge. There must, then, exist some other reason, and this would seem to lie in certain deficiencies in the education of the physician, deficiencies which are true in all countries but which are especially notable in America.

Mindful of this condition, medical educators have sought to correct it by demanding a certain amount of liberal arts study as a prerequisite to entrance into the medical school.

Most of our universities now require two years of college work, while some insist upon the possession of the degree of B.A. or B.S. Though the theory is excellent, in practice the present plan leaves very much to be desired. The freshman and sophomore years in most of our colleges are mainly occupied in stimulating the indolence acquired by the student during his senior year in high school, while the so popular elective system enables him to choose those courses which are best suited to leaving his mind at absolute rest.

Intellectual curiosity is not often awakened and, where only the first two years of college are required, the men have generally only partially completed any comprehensive courses they may have undertaken, and have not acquired much facility for scrutiny and analysis of their subject matter.

Then there are the four-year premedical courses, especially designed for those proposing to enter the field of medicine. These are as varied as the minds of the faculty groups who arrange them and, while in one college the emphasis is placed upon biology and allied matters, in another it may be organic chemistry, while some occupy the semester hours with anatomy, bacteriology and so on, all of which are repeated immediately the student begins his actual medical course.

This type of preliminary work simply accentuates the vocational training, later to be so greatly amplified in the school of medicine.

Insufficient, true formative education, together with the quite casual manner with which the student considers his intellectual obligations to himself, would seem to offer a fair explanation of our low cultural standards.

Happily, the correction of this somewhat depressing state of affairs offers but little difficulty, although perhaps a strong conviction on the part of the writer of the ease of bringing about the desired change, may have oversimplified it in his mind.

Either the University of Montpelier in about 1350, or that of Cologne a little later, set forth the conditions under which a degree of bachelor of arts might be conferred. A term of four years, each of two semesters, was the minimum requirement, and ever since this time, colleges and universities have continued the practice under identical conditions.

However, with the passage of the years, and especially since the "educational revolution in America" of the late eighties, and since the wide application of the elective system in our colleges, the amount of work required to obtain the various academic degrees has been steadily reduced, although the time elapsed remains constant.

In effect, then, rather than that the student be fully occupied to attain his education in four years, he is much concerned with social and athletic activities in order to fill his days.

The result is a very superficial structure of mental development, with a deterioration of the ability to concentrate and acquire the mental discipline so absolutely requisite for successful training in a profession.

These leisurely and so often unfruitful years are followed by the crowded curriculum of the medical school in which there is scarcely ever time for even a brief survey of correlated topics, not definitely related to medicine itself.

It is proposed that an entirely different educational program in colleges be inaugurated for such students as propose to pursue a professional career—be this medicine, law, engineering, or whatever.

There could be established a two-year course in cultural education, the work to be entirely completed within this time and the student graduated, with perhaps some academic recognition in the form of a new degree.

The subjects taught would include history, philosophy, the classics, languages, especially English, mathematics, and literature, with possibly a secondary group, as logic.

There would be no attempt to deal with either abstract or applied science unless one regards mathematics as a science rather than a philosophy. The roster would require many more hours in the classroom than at present, possibly

thirty-six or even forty hours weekly, this to be determined by trained educators. Since the medical student habitually spends considerably more time than this in his daily work, the intensity of such a course would develop in the student the ability to study and the so necessary mental discipline referred to before.

Our absurdly long vacations could well be shortened, the months of July and August being generally the only period when the heat of summer makes mental or physical concentration difficult in America.

One can visualize the graduate of such a course of study as a man who has been given an insight into the thoughts and practice of foregoing generations and who has learned the proper method of study and who happily has had the golden gates of the world's literature opened to him. Now, stimulated and eager, our student enters medical school, not for four years, but for six, the total period of university life thus remaining unchanged.

The first two years of the medical course would be in effect a transition between the cultural studies which have preceded it and the definitive medical work to follow. Psychology, sociology, genetics and the laws of heredity, general biology with comparative anatomy and physiology, and many other subjects germane to medicine and of inestimable value to the doctor would be taught by highly qualified scientists.

The beginnings of the basic sciences would be incorporated in this first two years, after which the usual medical curriculum would follow for the remaining four years.

By such a plan, many of the present gaps in the mental equipment might well be eliminated and the resulting product, it is hoped, would be a physician of far wider horizons, capable of acute cultural analysis such as now belongs only to the few.

This whole matter of medical pedagogy is so fascinating that it is difficult to close its discussion.

The prevalent view, for example, is that if a man of outstanding investigative ability be secured to head a department, the institution obtaining his services is fortunate. Sometimes this is true, but more often such a man surrounds himself with like-minded persons, and while the research work proceeds apace with admirable results, the pedestrian, dull teaching of undergraduate students the facts of medicine, is often neglected to an unbelievable degree.

Despite any opinion to the contrary very, very much of medical knowledge consists of apparently unrelated facts which, to be known, must be studied and memorized, and in which no amount of inductive reasoning is of any avail whatsoever.

The necessity of training teachers of medicine to teach is very real—and is far too casually considered not only in America, but in Europe as well.

The suggestions here made may be the idle dream of an old fellow whose teaching days have long gone by but, if there has been expressed but the tiny germ of an idea which may stimulate wiser heads to give it some thought and perhaps to amplify it to a usable plan, he will remain well content.

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HYDRAMNIOS*

The Joseph Brettauer Memorial Lecture

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FIRST of all, I want to tell you how much I appreciate the very great honor you have conferred on British gynecology and on me personally by inviting me to come to this great country to deliver the Joseph Brettauer address. I feel the honor is even greater by the fact that it has been made a second time, the first time being somewhat unpropitious for travel, at any rate for those of us who were then on the other side of the Atlantic Ocean.

I have chosen as my subject for this address, "Hydramnios." Pundits tell me the word is really "hydramnion," but I am going to persist in using the more common, although possibly inaccurate word, "hydramnios."

In 1933, at the Congress of Gynecologists and Obstetricians of the British Empire, held at Birmingham, I read a short paper describing a few cases and advocating the general adoption of the treatment that I had found successful. Although many obstetricians seem to have heard of this treatment, I find exceedingly few ever use it, and I am hoping, as a result of this paper, to spread the gospel somewhat.

Hydramnios is vaguely defined as being a great excess of liquor amnii. Most authorities say that the normal amount of liquor amnii is about 1 to 2 pints (600 to 1,200 c.c.), but it has never been definitely laid down exactly how much must be present before the transition from excessive liquor to hydramnios takes place. From a practical point of view, the exact amount is not important, as the condition of hydramnios is usually such an enormous excess that there is no doubt at all. I think no one will quibble if I define it as when the amount of liquor exceeds 5 pints (3,000 c.c.).

Many suggestions have been put forward as to the cause of this great excess of liquor. In roughly 50 per cent of cases we find gross fetal maldevelopment, anencephaly, spina bifida, stenosis of the esophagus, hydrocephaly and twins, this last one being common and usually associated with two normally developed babies. We are still left with about 50 per cent of cases in which we can find no cause whatsoever. In one well-known manual of obstetrics, edited by Eardley Holland,[1] it is stated that when hydramnios occurs in a sac of one of twins, there is no doubt that the source of the excessive liquor is fetal urine,[1] but no evidence whatsoever is produced of the grounds on which this very unlikely opinion is founded.

I have tried injecting indigo, carmine, and insulin into the amniotic sac and looking for evidence that either was absorbed by the mother, and failed to find any.[2] DeLee[3] administered methylene blue to the mother and found it appeared in the fetal urine, but not in the liquor amnii.

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Incidence.—Hydramnios occurs about once in two hundred pregnancies. It has been estimated as occurring in anything ranging from one in one hundred to one in three hundred, but usually the estimates are made on a comparatively small series when a variation of one or two may make a very great difference to the answer. It appears most commonly to be found between the twentieth and twenty-eighth week of gestation, but in some cases the great excess does not cause maternal distress until the last four or five weeks. When the amount of liquor exceeds 5 pints (3,000 c.c.), it is likely to cause marked maternal distress, not only physical discomfort, but cardiac and respiratory embarrassment and edema and, rarely, albuminuria, and it is usually obvious that something must be done. I find the usual treatment everywhere is to puncture the membrane through the cervical canal, either by direct puncture or by high puncture with a metal catheter. This method is not always successful as, when hydramnios affects one of twins, it is always the sac which is lying in the upper part of the uterus that becomes distended, and puncture of the membrane of the nonhydramniotic sac does not give immediate relief, but only produces the second effect of interference via the cervix, namely, the onset of labor. As the majority of cases occur before viability of the fetus, this method of treatment inevitably kills the baby or babies.

In 1912, Wormser[4] in Germany described that he had punctured an amniotic sac via the abdomen—not in a case of hydramnios. In 1933, I published a paper[2] in which I described a method of treating hydramnios by puncturing the amniotic sac and withdrawing the excessive liquor. The method is as follows: about one hour before the procedure, ⅓ grain of omnopon and $\frac{1}{150}$ grain of scopolamine are administered and the patient kept quietly in bed. A spinal trocar and cannula is prepared (I use this instrument as I find its length, 3 inches, is about right, and it has a fairly large bore). A collecting bottle, lengths of rubber tube, and a suction pump are also required. With the patient lying on her back the abdomen is palpated and an area chosen, usually above the umbilicus, where there is marked fluctuation and where fetal parts cannot be palpated. The skin is prepared over this area by painting with iodine. A skin puncture is made with a small tenotomy knife and the cannula inserted through the abdominal wall, through the uterus, and into the amniotic sac. On withdrawing the trocar it can be observed that the liquor is very rarely under pressure, it usually drips out quite slowly, so the cannula is attached to the suction pump via the collecting bottle and as much liquor as possible is withdrawn.

The most I have withdrawn at one operation was twelve and one-half pints—over a gallon and one-half, or seven and one-half liters. The patient was much more comfortable after it and did not go into labor, and later had a normal live baby. When no more liquor can be withdrawn, the abdomen is palpated to ascertain whether or not there is still an excessive amount and, if so, the trocar and cannula are inserted in a different place and more withdrawn. When no more can be withdrawn, a dressing is applied and the patient is returned to her room; one-fourth of a grain of morphia is administered and repeated that evening and again the following morning, to discourage uterine contractions. A certain number of cases do go into labor: a certain number do not.

In most cases the excess of liquor will reaccumulate in three or four weeks, and the whole procedure can be repeated again and again. Some cases do not produce further hydramnios and I do not know why. I saw one patient about thirty weeks pregnant, and withdraw nine pints of liquid. Nine weeks later she had a normal spontaneous delivery of a normal live baby. I saw another case in 1942, a primigravida 25 years of age, whose last menstrual period had been twenty-one weeks previously. She complained that during the past two weeks her abdomen had increased enormously in size, and she was in great discomfort. On palpation, the uterus reached to the ensiform cartilage, and the abdomen measured 36 inches in circumference at the level of the umbilicus. An x-ray disclosed twins but, as this early stage of pregnancy, it was not possible to determine whether or not fetal abnormality was present. Seven pints of liquor were withdrawn. Three weeks later she was again in great discomfort, and I withdrew 9 pints. Four weeks later I withdrew 11 pints, and six weeks later again 11 pints; a total of 38 pints (23 liters). Ten days later she went into spontaneous labor, thirty-six weeks after her last period, and had a normal labor; the first twin weighed 2 lb., 7 oz. (1,170 Gm.), and was stillborn, having obviously died during labor, as evidenced by early maceration; the second twin weighed 3 lb., 9 oz. (1,710 Gm.), cried spontaneously, and did well. Twenty-eight days later the baby was discharged, weighing over 5 lb. (2,400 Gm.).

Dangers and Difficulties.—I have been told that this method is very dangerous. There is a risk of carrying virulent infection into the uterine cavity. There is a risk that the trocar and cannula may perforate the mother's intestine and set up fatal peritonitis. There is a risk that the large blood vessel in the uterine wall may be perforated and cause hemorrhage. There is a risk that the trocar and cannula may seriously injure the fetus (perforate an eye for instance). There is a risk that the placental attachment may be separated with serious bleeding. Not one of these things has occurred. It is far easier to surgically sterilize the skin of the abdominal wall than it is to sterilize the vaginal vault and cervix. It is unknown to find intestine in front of a uterus of this size unless it is tethered there by adhesions from a previous operation, and anyway it is easy to detect it if it is there by simple palpation and percussion. I have pricked blood vessels on several occasions, the only trouble I have found is when I withdraw blood-stained liquor or even blood, which tends to clot in the needle. There have been no ill-effects that could be shown due to this accident at all. Palpation and selecting an area where fetal parts are not immediately under the uterine wall remove any chance of injuring the fetus. Separation of the placenta has probably occurred in one or two cases as a stillborn baby is eventually born and the placenta is found to be extensively fibrosed—so in my experience these theoretical dangers do not actually ever occur.

Results

After eliminating cases in which the first aspiration was performed later than thirty-five weeks' gestation, I find that live babies resulted in over 25 per cent of cases which required some treatment before viability of the fetus. In all

these cases, relieving the tension by puncture of the membrane via the cervix would inevitably have brought on labor with death of the fetus.

In conclusion, there is obviously much room for research into the cause or causes of hydramnios.

In the few cases in which I have had an Rh negative factor, it seems to have no bearing at all.

In view of the fact that at any rate a certain number of babies' lives can be saved, I do ask you all to give this method of treatment a fair trial. My series is only about 50 cases. That is really too small for a final pronouncement, and in this country it should not take long to get sufficient numbers to prove its value or otherwise.

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135 HARLEY STREET

CORPUS CARCINOMA

A Study of Three Hundred Twenty-Two Cases*

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PHYSICIANS charged with the responsibility of treating carcinoma patients in large numbers are constantly seeking to improve existing therapeutic methods with the hope of prolonging the survival period. For nearly half a century hysterectomy has been accepted as the preferred treatment for corpus carcinoma. The results from operation alone were generally viewed with optimism, the impression being—and it was only an impression—that hysterectomy offered an extremely favorable prognosis. With the advent of follow-up studies this optimism gradually dwindled. Incomplete hysterectomy was proved unsatisfactory and total hysterectomy is now recognized as no cure-all in these cases. About 1925 radium was replacing radical hysterectomy as the preferred method of treatment for cervix cancer. Because of its successful use in this connection, it was also tried in corpus carcinoma. But, since its use was largely confined to advanced cases, it is not surprising that the results were equivocal. While irradiation did not cure many advanced cancers of the uterine body, the fact that it prolonged life and cured some was important. That corpus carcinoma could be seriouly damaged nad occasionally destroyed by the use of radium, x-ray, or both, had now been demonstrated. From these early experiences came the seeds from which grew the methods of combined therapy in use today. Since this early trial period many excellent contributions on the subject have appeared in the literature, and we regret that lack of space and time does not permit their well-deserved recapitulation in this report. Because early experience foreshadowed definite benefits from irradiation in the management of corpus carcinoma, this whole problem was carefully considered by us in 1931 at the time our Gynecology Tumor Conference was first organized. As a result of our deliberations, a preferred program of treatment was outlined. The plan was based on the following assumptions.

1. Elimination of the primary neoplasm could probably best be achieved through complete surgical extirpation of the entire uterus, tubes, and ovaries.
2. Theoretically, supplemental irradiation therapy should be most beneficial when given prior to operation. By so doing we hoped to: (a) cause widespread damage to cancer cells; (b) minimize manipulative spread at the time of operation; (c) obliterate lymphatics (something which now, fifteen years later, we know is only partially accomplished).
3. Since we were not depending upon irradiation for destruction of the primary lesion, and since a damaging effect on outlying cancer cells was our aim in using preoperative irradiation, it was agreed that deep x-ray therapy followed

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later by adequate surgery should be our planned treatment of choice. The decision to use preoperative deep x-ray therapy in preference to radium was based on its known effectiveness in cervix neoplasia and its helpfulness in prolonging life in some ovarian carcinomas. Furthermore, we believed that the broader fields affected by the use of irradiation might also damage neoplastic cell masses sometimes found in the tubes and ovaries of corpus carcinoma patients (seven times in our operated cases).

During the fourteen and one-half years since the inception of this program of treatment in 1931, we have had under our care 322 patients with corpus carcinoma. All these individuals have been carefully studied, and data concerning their treatment and progress recorded on punch cards suitable for statistical evaluation in International Business Machines. All patients have been traced, there are no untraced cases.

Since the University of Michigan Hospital is a State-owned institution primarily for the care of indigent patients from outlying districts, it is obvious that many of our corpus cases were advanced and beyond surgical help when admitted. These advanced patients, and others considered excessively poor operative risks, were treated entirely by irradiation usually a combination of x-ray and radium.

TABLE I. METHODS OF TREATMENT USED IN THE CARE OF 322 PATIENTS WITH CORPUS CARCINOMA

	A		*B*					
			SURVIVAL RATES IN PER CENT OF THOSE ELIGIBLE					
			3 YEAR		5 YEAR		10 YEAR	
TREATMENT	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	21	6.5						
Radium	37	11.4	34	44.1	29	41.3	10	30.0
X-ray	32	9.8	30	23.3	22	27.2	6	16.6
X-ray and radium	89	27.4	65	33.3	50	28.0	26	23.0
Surgery	20	6.2	18	66.6	15	53.3	8	50.8
Radium and surgery	16	4.9	14	87.5	13	86.6	9	81.8
X-ray and surgery	96	29.5	79	84.7	61	77.0	23	65.0
X-ray, radium and surgery	11	3.6	7	70.0	4	66.6	3	60.0

Ninety-six, or 29.5 per cent, were treated according to plan; namely, preoperative deep x-ray therapy followed in six weeks by adequate surgery. This represents the largest treatment group in this series.

The type and the number of patients in each category are shown in Table I.

The factors generally used in the x-ray treatment were as follows:

Two hundred kilovolt peak radiation filtered by 0.5 mm. copper and 1.0 mm. aluminum, half value layer (h.v.l.) 0.9 mm. copper, distance, 50 cm. minute output about 50 roentgens as measured in air. Two anterior and two posterior pelvic fields 12 by 15 cm. to 15 by 15 cm. in size. The beam was directed at an angle through each field so as to cross-fire the uterine corpus. Two hundred roentgens as measured in air were given to each of two fields daily to a total dose of 2,000 to 2,200 roentgens per field.

The radium factors were:

Brass tandem applicator of either two or three chambers depending on the length of the uterine canal. Total filtration was equivalent to 0.5 mm. of platinum. Each chamber might contain from 30 to 50 mg. of radium. The radium dose per chamber varied from 1,500 to 2,400 mg. hr., the lower part of this range was employed when a two-chambered tandem was used, and the higher part with a three-chambered tandem. Occasionally, vaginal applicators placed in the lateral fornices were also used.

Many things influence the results of treatment and all deserve mention. In this connection it was of interest to learn whether, as a result of cancer education, patients were consulting physicians earlier than formerly. As shown in Table II, our study revealed no recent improvement in this respect.

TABLE II. TIME WASTE FROM ONSET OF FIRST SYMPTOM TO BEGINNING OF TREATMENT

REPORTED BY	YEAR	TIME WASTE
Miller[1]	1929	24.0 months
Collins[2]	1934	11.1 months
Miller[3]	1940	12.7 months
Miller and Henderson (this report)	1946	12.5 months

The average time lapse from the onset of symptoms to the beginning of treatment is significant. Corpus carcinoma occurs most frequently in women past the menopause, the average age in our series being 54 years. Consequently, the appearance of spotting or abnormal discharge at the average age of 54 years should be sufficiently unusual to cause concern. Apparently there still is great need for cancer education among women of this age group. This time waste factor, though significant, does not always indicate the extent of the lesion.

While clinical grouping of these cases is not very satisfactory, helpful information may be gained by determining uterine size, a tangible factor which serves as the criterion for most clinical classifications of corpus carcinoma. The clinical grouping of 301 patients in our series is shown in Table III.

TABLE III. CLINICAL GROUPING OF 301 CORPUS CARCINOMA CASES

	GROUP I		GROUP II		GROUP III		UNKNOWN	
TREATMENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Radium	6	16.2	24	64.8	7	18.9	0	0
X-ray	5	15.6	11	34.2	6	18.7	10	31.2
Radium and x-ray	25	28.0	45	50.5	15	16.8	4	4.4
Surgery	2	10.0	10	50.0	8	40.0	0	0
Radium and surgery	5	31.2	8	50.0	3	28.8	0	0
X-ray and surgery	40	41.6	50	52.0	6	6.1	0	0
Radium, x-ray and surgery	3	27.2	5	45.6	3	27.2	0	0
Total	86		153		48		14	

Our clinical classification was based on the following:

Group I.—No palpable enlargement of uterus.

Group II.—Moderate enlargement of the uterus up to the size of a two-and-one-half-month pregnancy.

Group III.—A large uterus—the size of a three-month pregnancy or greater.

TABLE IV. HISTOLOGIC GRADE—301 CASES CORPUS CARCINOMA

TREATMENT	GRADE I		GRADE II		GRADE III		GRADE IV		NOT GRADED	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Radium	1	2.7	19	51.3	14	37.9	1	2.7	2	5.4
X-ray	0	0	9	28.1	16	50.0	2	6.2	5	15.6
Radium and x-ray	2	2.2	51	57.3	25	28.0	6	6.6	5	5.5
Surgery	2	10.0	14	70.0	4	20.0	0	0	0	0
Radium and surgery	2	12.5	9	56.2	3	18.7	1	6.2	1	6.2
X-ray and surgery	2	2.0	58	60.4	32	32.2	2	2.0	2	2.0
Radium, x-ray and surgery	1	9.2	5	45.4	5	45.4	0	0	0	0

The histologic grade is shown in Table IV.

While histologic grading of endometrial carcinoma does not necessarily indicate prognosis, experience has shown that there is some difference in the rate of growth, invasiveness, and spread between the less-differentiated and the highly-differentiated carcinomas. Histologic grade, therefore, is a factor in determining survival rate.

In evaluating results of treatment, it should be noted that our survival rates are uncorrected. In studies involving older patients such as this, correction for noncarcinoma deaths will some day be desirable. This is not yet done customarily, and was not done in this report.

There appears to be little reason for more than passing consideration of our cases treated by irradiation alone. In the groups so treated were the advanced cases, the extremely obese patients, and, of course, the very poor surgical risks. The fact that in these groups treated by means of irradiation it was possible to attain approximately a 20 per cent ten-year salvage rate is significant and reason for recognizing in irradiation therapy, be it intracavitary radium or x-irradiation, a potent and valuable adjuvant to surgery in the management of corpus carcinoma. This fact was clearly shown in a compilation of results by several workers reported by Corscaden[4] in 1944. Tables V, VI, and VII are modified from Corscaden's report, and deal with operable cases. They indicate what may be expected by the various therapeutic methods or combinations thereof.

While there appears to be no objection to the combined preoperative use of both x-ray and radium, in the past most studies have dealt with only a single form of preoperative irradiation. Perhaps this is fortunate, since it permits better evaluation of their respective merits when used in this connection. That both forms of irradiation can be extremely helpful in the control of corpus carcinoma has been frequently demonstrated.

In 1941 Wintz[5] reported a five-year survival rate of 69.1 per cent in 127 operable cases treated by x-ray alone. In the same year Hurdon[6] announced a 62.0 per cent five-year salvage rate in 40 patients treated with radium alone. While these are selected figures and probably represent the most optimistic results obtained from the use of these therapeutic weapons, the literature abundantly attests the effectiveness of irradiation in the control of corpus carcinoma. Used alone, neither radium nor x-ray appears to equal the results obtained by surgery, but when combined with surgery—especially as a preoperative mea-

TABLE V. CARCINOMA OF THE CORPUS UTERI*
INTRAUTERINE RADIUM

REPORT BY	NUMBER TREATED	PER CENT FIVE-YEAR SURVIVALS	
Heyman	186	35.5	46.4
Fricke and Bowing	16	50.0	
Fricke and Heilman	76	52.6	
Healy and Brown	64	58.0	
Hurdon	40	62.0	
Corscaden	27	48.0	
Total	409		

*Modified from J. A. Corscaden, J.A.M.A., Dec., 1944.

TABLE VI. CARCINOMA OF THE CORPUS UTERI*
HYSTERECTOMY

REPORT BY	NUMBER TREATED	PER CENT FIVE-YEAR SURVIVALS	
Pleiderer	153	51.5	57.8
Von Mikulicz and Volbracht	133	54.1	
Norris and Dunne	115	47.8	
Masson	306	66.6	
Total	707		

*Modified from J. A. Corscaden, J.A.M.A., Dec., 1944.

TABLE VII. CARCINOMA OF THE CORPUS UTERI
RADIUM FOLLOWED BY HYSTERECTOMY

REPORT BY	NUMBER TREATED	PER CENT FIVE-YEAR SURVIVALS	
Healy and Brown	93	55.0	65.3
Heyman	65	78.0	
Ward and Sackett	21	57.1	
Newell and Crossen	19	63.2	
Morton	18	61.1	
Arneson	10	90.0	
Corscaden	25	72.0	
Total	251		

*Modified from J. A. Corscaden, J.A.M.A., Dec., 1944.

sure—the prospects appear very promising. In 1936 Arneson[7] reported a 90 per cent five-year survival rate for corpus carcinoma following the use of intracavitary radium and surgery. Scheffey, Thudium, Farell, and Hahn,[8] also report a 90 per cent five-year survival rate following the use of radium and surgery.

These are truly amazing figures, especially since death from natural causes in women of average corpus carcinoma age might well be enough materially to influence survival rate during a five-year period. Were it not that both reports are based on a small number of cases, it would appear that we need search no further for an entirely satisfactory treatment. When, however, collected results obtained from the preoperative use of radium followed by surgery are reviewed, the picture is not nearly so striking (Table VIII).

While our own experience with the use of preoperative radium in corpus cases has likewise been good, the number of cases so treated is again too small to permit conclusions. In sixteen patients so treated, there were 86.6 per cent five-year survivors. (See Table I-B.)

TABLE VIII. COMPOSITE TABLE SHOWING SURVIVAL RATES FOLLOWING DIFFERENT FORMS OF TREATMENT FOR CORPUS CARCINOMA*

TREATMENT	NO. OF CASES	SURVIVAL RATE IN PER CENT	
		5 YEAR	10 YEAR
Surgery	707	57.8	
Radium	409	46.4	
Radium and surgery	251	65.3	
X-ray and surgery	96	77.0	65.0

*Compiled from Corscaden's report and our own data.

For reasons already stated, our treatment of choice during the past fourteen and one-half years has been deep x-ray therapy followed by surgery six weeks after completion of the x-irradiation. Results achieved by this combination based on 96 cases are shown in Table I-B, and for convenience are repeated here, thus:

84.7 per cent three-year survivors.
77.0 per cent five-year survivors.
65.0 per cent ten-year survivors.

Table VIII represents an attempt to compare results by the several methods of treatment now in common usage. Obviously, the inequality in the number of cases in the various groups lays this comparison open to criticism.

There was one postoperative death among our 96 patients treated by preoperative x-ray and surgery. This occurred on the tenth day and was due to pulmonary embolism.

The uterus, tubes, and ovaries of these 96 patients were abundantly blocked for study purposes. Fifteen, or 15.6 per cent, revealed no carcinoma. This is less than has been reported following the use of intracavitary radium (24 per cent to 75 per cent), but it should be recalled that we did not depend upon irradiation for destruction of the primary lesion.

The effectiveness of intracavitary radium is variable and inconsistent. Gray, Friedman, and Randall[9] have shown that the carcinoma may persist even after very heavy treatment with radium.

While the significant factual data of our study have been stated, there remain the impressions—thoughts which bud during every study only to disappear or else grow into something more than an impression—the fruits of experience.

To list them is to risk being dogmatic. Even so, this is the way things appear to us:

1. Preoperative x-ray has proved to be a valuable adjuvant to total hysterectomy and bilateral salpingo-oophorectomy in the treatment of corpus carcinoma.
2. Its use clears up uterine infection, reduces uterine size, and decreases pelvic hyperemia, thereby facilitating operation.
3. Preoperative x-ray has not in any discernible way interfered with wound healing.
4. The three weeks required for its administration is a drawback, but by no means a serious one, since for most patients this is an outpatient procedure.
5. The results obtained from preoperative x-ray warrant its continued use, at least until some other combination or new form of therapy is proved more satisfactory.

6. The use of very high voltage x-ray as a preoperative measure in corpus carcinoma appears promising and should be explored further.

7. Radium, likewise, gives good results, but, on the basis of available data, we do not believe the relative merits of preoperative x-ray versus radium can be accurately stated.

8. We hold no special brief for any form of therapy. Our interest in and work with deep x-ray as a preoperative measure in corpus carcinoma was entirely with the hope of increasing our survival rate.

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Discussion

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—This discussion is based upon a study of 93 patients at Johns Hopkins Hospital with adenocarcinoma of the corpus uteri. We have divided these patients into two groups, namely, those that are poor and those that are good surgical risks. The reason for this is quite obvious, for the debilitated, elderly patient is treated with irradiation alone while those in the good risk group receive a course of intracavitary radiation which is followed by a panhysterectomy and a bilateral salpingo-oophorectomy.

The plan of procedure in the poor risk group is as follows: Diagnosis is determined by careful curettage of the body so as not to disseminate infection which is frequently associated with the malignancy. The size of the uterus is then determined, for the enlarged uterus as a rule bespeaks advanced disease with myometrial involvement. Several sacs of radium, each containing 25 mg., are then introduced into the uterus until the cavity is filled; four to five sacs may thus be used. These sacs are removed in an order in reverse to their introduction, for otherwise a so-called "log jam" may occur and thus render their removal difficult. This difficulty occurred in one patient necessitating the removal of the radium under pentothal anesthesia. These debilitated poor risk patients receive, as a rule, 4,000 to 4,500 mg. hr. of radium. Following this the patient is given a cycle of deep x-ray therapy through four portals to the amount of 8,000 roentgens. We have reviewed 46 patients that were so treated, and find that the salvage rate at the end of four years and seven months is 28.3 per cent.

The method of therapy and results of patients in the good risk group which number 47 is as follows: the preliminary phases of therapy, i.e., dilatation and curettage, pathologic diagnosis, and intracavitary radiation are the same as in the poor risk patient, the dosage of radium applied in multiple sacs being 4,000 to 4,500 mg. hr. Approximately four to five weeks later a panhysterectomy and bilateral salpingectomy are done. An important and well-recognized preliminary step is clamping the isthmic portion of the Fallopian tubes so as to prevent expulsion of malignant cells into the peritoneal cavity. After intracavitary radiation, how soon should the panhysterectomy be performed? This is a moot point. We feel that lines of cleavage are dissipated and the tissues become more fibrous and less workable if we delay longer than four to six weeks. It would seem that intracavitary radiation does increase somewhat the operative difficulty but, in spite of this, we have had no operative accidents, i.e., bladder or ureteral fistulas, nor have we had an operative death. In this good risk group we have reviewed 47 patients treated by this combination method of therapy and

we find that at the end of four years and seven months we have a survival rate of 76.7 per cent. This figure vividly demonstrates the advantages of intracavitary radiation plus panhysterectomy over irradiation therapy alone.

All of the 93 patients reviewed had a microscopic grading and we found that the majority fell in the grades II and III and, as expected, the more anaplastic the growth, the more quickly it disappeared.

A recent report by Stowe (AM. J. OBST. & GYNEC. 51: 57, 1946) on residual growth in the uterine musculature following adequate intracavitary radiation is most illuminating. He reported 53 patients with corpus carcinoma who had been treated by the above-mentioned combination method of therapy, and found that 50.9 showed residual carcinoma in the myometrium. He was of the opinion that operative removal of the organ was of vital importance.

At present we are restudying the radiated uteri, and the examination of multiple sections may confirm Stowe's report.

We prefer intracavitary radiation, for we feel that the radium applicator can be directly applied to the lesion. However, the results presented by Dr. Miller show that equally good results may be obtained with the use of deep x-ray therapy.

DR. FRANK A. PEMBERTON, Boston, Mass.—Up to 1936 we treated 294 of a total of 307 cases of carcinoma of the endometrium at the Free Hospital for Women. Varying sequences of x-ray, radium, and operation, as well as operation alone, were used. There are not enough cases in each group to make useful comparisons, but the total results are shown in the tables below:

Total	307	Five-year salvage	55.7 per cent
Treated	294	Five-year salvage	58.1 per cent
Total eligible		Ten-year salvage	43.5 per cent
Treated eligible		Ten-year salvage	45.4 per cent

From 1936 to 1941, 108 cases were treated with the following results:

X-ray and radium	No. 27	Five-year salvage	12 (45 per cent)
Hysterectomy, radium, and x-ray	No. 66	Five-year salvage	43 (66 per cent)
Hysterectomy	No. 15	Five-year salvage	9 (60 per cent)
Total	No. 108	Five-year salvage	64 (59 per cent)

In the first series there was a five-year salvage of 58.1 per cent, and ten-year salvage of those eligible of 45.4 per cent. The five-year salvage in the second series is about the same. The figure of 45 per cent for the cases treated by radiation alone is rather high, but is due to there being several early cases in these patients who are poor risks. We operate on every case where it is possible.

Twenty-eight of these 66 patients had hysterectomy first, then radium in the vagina, and x-ray externally; intrauterine radium followed by operation and x-ray in 23; and intrauterine radium followed by operation in fifteen. Bilateral salpingo-oophorectomy was always combined with the complete hysterectomy. There were 15 cases in which hysterectomy alone was done, with a 60 per cent five-year survival.

Now it seems reasonable that if these 66 cases and those treated by operation alone had all received radiation before operation, the results would have been better.

Since Healy's report in 1939 of a 79 per cent five-year salvage in 28 cases so treated, and Miller's report in 1940 of his success with preoperative x-ray, we have used preoperative radiation more extensively, and our impression is that the results are more favorable.

We feel that intrauterine radium as well as x-ray should be preferable to x-ray alone, because there is bound to be some squeezing of the uterus during operation, even though it is held by clamps down the broad ligaments and never with a double hook or uterine clamp on the fundus. The cells are devitalized if enough radium is given. They get from 3,000 to 5,000 roentgens of x-ray. The intrauterine radium should devitalize the cells of the local growth, and there should be less chance of spreading them during the manipulations.

An objection to the use of intracavitary radium is that if the tumor is infected or there is enough stenosis of the cervix to have caused pyometra, the application may stir up and

spread sepsis. One of these patients died from such infection after the application of radium. One died from a lung abscess three and a half months after operation. Therefore, x-ray alone is preferable under such conditions as a preoperative treatment. But our feeling at the present time is that preoperative radiation is most important, and that radium should be given as well as x-ray in most cases.

DR. L. C. SCHEFFEY, Philadelphia, Pa.—Since the work of our clinic at Jefferson was presented before the Obstetrical Society of Philadelphia this spring and the paper published in the JOURNAL (52: 529, 1946), I shall refer only briefly to our experience at this time, quoting from several of our tables.

Table I refers to the patients seen, treated, and followed up, showing that 104 are eligible for five-year statistics.

Table II refers to the results obtained with a planned technique of preliminary intrauterine radium followed by total hysterectomy and bilateral salpingo-oophorectomy, eight to twelve weeks later. We do not feel that the preoperative radium destroys the malignancy locally; in fact, over 50 per cent of the removed uteri show residual carcinoma. We are convinced, however, that the lesion is devitalized as shown on the photomicrographic slides; that this lessens the chance of cancer-cell distribution at the time of operation, and that vaginal vault recurrence is less likely, for we have seen none to date. Neither has there been any primary mortality in the series.

Whether preliminary radium is preferable to preliminary x-ray is debatable. We would not hesitate to use x-ray postoperatively if there is evidence of extension from the uterus at the time of operation. In this series, no x-ray was used either preoperatively or postoperatively. There will be certain cases, of course, in which the size of the uterus and the contour of the endometrial cavity, particularly where concomitant myomas are present, that preclude the application of intrauterine radium units. In such instances we have proceeded immediately with total hysterectomy and adnexal removal, either with a frozen section report of the curettage, or merely with a suspicion of fundal carcinoma being associated with the uterine myomas.

Table III shows the comparative results obtained with (1) surgery alone (adequate and inadequate); (2) irradiation alone (radium and/or x-ray); (3) an unplanned technique (surgery, adequate or inadequate, combined with radium and/or x-ray in varied sequence); (4) the planned technique (as shown in Table II). The superiority of the latter, at least in our hands, seems striking.

The survival figure after irradiation corresponds fairly closely with the figures showing the percentage of previously irradiated uteri with residual carcinoma. This offers some consolation to ourselves and to the patient in those instances where irradiation has to be relied upon, because subsequent operation is contraindicated for well-known reasons. In other words, irradiation alone seems to offer a 40 to 50 per cent chance of five-year survival when surgery is impossible or inadvisable.

The notation regarding primary mortality needs some explanation. There were two deaths in 87 patients in whom surgery played a part in treatment, either alone or in conjunction with irradiation; in 8 of these patients it was not possible to remove the uterus at operation. Of the remaining 79 patients, the uterus was removed, but five of the 79 patients had received either primary or subsequent treatment elsewhere, leaving 74 patients who were treated solely at Jefferson. This accounts for the slight variation in the mortality percentage which is based solely on the same two deaths among the entire group of 87 patients not receiving the planned technique of treatment displayed in Table II, and shown for comparison in Table III with no primary mortality.

DR. GEORGE GRAY WARD, New York, N. Y.—Since 1919, we have had under our direction at the Woman's Hospital 243 cases of carcinoma of the corpus uteri.

We believe surgery is the most important factor in the treatment of this disease. Irradiation is a valuable adjunct. Preoperative irradiation is the most desirable technique. The question as to whether it is better to use irradiation in the form of radium or deep x-ray is open to discussion.

Microscopic examination of the growth is essential for an accurate diagnosis, and a suction biopsy or a diagnostic curettage is necessary to procure the tissue. Suction biopsy may fail to reveal a small area of carcinoma in the cornua or in an irregular cavity. A proper curettage is less likely to give a negative finding. I prefer to do a curettage, and at the same sitting take advantage of the opportunity to introduce radium to render the tumor cells inactive as soon as possible. Should a six-hour report be negative, the radium may be removed at once, otherwise, 2,400 to 3,600 mg. hr. are given. A complete hysterectomy and salpingo-oophorectomy follows in from two to four weeks, after which a series of deep x-rays is given by the Coutard technique, which takes from twenty-five to thirty days.

It seems to me that there is less delay by using a radium application first, except in cases where the disease has extended beyond the uterus and an hysterectomy is not feasible.

In 1942, I gave a report of our five-year survivals in 142 cases of corpus carcinoma. The absolute survival rate was 44.4 per cent. Since then we have had a five-year follow-up of 38 cases. Of these, 21 are alive and well, and there were 17 deaths, or an absolute survival rate of 55.2 per cent. In the 17 deaths, eight were considered favorable for irradiation and hysterectomy. Nine were in advanced stages of the disease with metastases and unsuitable for operation, from senility, diabetes, or cardiovascular disease, etc. Of the eight favorable cases, two lived five years, but died of cancer.

In the advanced cases, one died of coronary thrombosis two months after radiation and one died of acute appendicitis.

The proportion of advanced cases seen in a series influences the absolute survival rate. Each patient with carcinoma of the corpus uteri must be individualized and treated according to the conditions present to obtain the best results.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I would like to discuss a limited series of cases. Within the last month I saw in my office patients treated for carcinoma of the uterine fundus during 1938. All were of the number one clinical group with the uterus about normal in size. We do not obtain a microscopic grading from our pathologist because he does not believe the grading is accurate. We do believe the clinical grading judged by the clinical extent of the disease is most important, and at least equally important to the microscopic grading. When we speak of wanting to get our patients early, I believe we really refer to the clinical grading.

Of the eight patients personally operated upon and managed during 1938, seven are alive and well without symptoms or signs of recurrence. One patient developed ascites and other evidence of recurrence and died within one year of operation and treatment. We believe that those who do die from recurrence of the carcinoma are likely to die early, and, if they survive a few years without recurrence, the prognosis immediately is good.

Our method of treatment at Harper Hospital is this: We like to employ preoperative radiation with both radium and x-ray. In each case we individualize and consult our radiotherapist. The intrauterine dosage of radium is never less than 3,600 milligram hours. A very fleshy patient may be given a larger dose of radium, since we do not feel so confident about the efficacy of x-ray in a fleshy patient. The x-ray radiation is administered by a supervoltage machine, 600,000 voltage constant. The deep x-ray therapy is given over a period of four or five days, and not over a period of three weeks as used by Dr. Miller. We are cognizant of the criticism of large radiation doses in some clinics. We are not, however, afraid to use large dosage and believe the nature of the disease justifies heroic measures. After hysterectomy, which is performed about eight weeks after the preliminary radiation, a second course of deep x-ray therapy is given.

CLINICAL AND PATHOLOGIC ASPECTS OF PRIMARY SARCOMA OF THE UTERINE TUBE*

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THAT primary sarcoma of the uterine tube is an unusually rare lesion is borne out by the fact that thus far only 21 cases have been specifically mentioned in the literature throughout a period of sixty years. Little detailed information exists in gynecologic texts. Furthermore, it is an unusual coincidence that Senger reported the first case in 1886, in the same year that Orthmann called attention to the first authenticated primary carcinoma of the tube. Since then, approximately 578 tubal carcinomas have been reported, a ratio to tubal sarcoma of about 25 to 1. Secondary sarcoma of the tube is even less frequently mentioned.

My interest (L. C. S.), and that of our former resident, Dr. Warren R. Lang, in this uncommon condition, was initiated by personal experience with such a patient, who was first seen by Dr. Fred B. Nugent. The case history is presented herewith.

Case Report

C. K., aged 70 years, para i, gravida i, was admitted to the private gynecologic service of the senior author at Jefferson Medical College Hospital on March 6, 1944. She complained of low pelvic pain and sensitivity, with intermittent vaginal discharge, sometimes bloody. The family history was essentially negative. Appendicectomy with drainage had been performed in 1932. Apart from "heart trouble," noted several years prior to admission, there were no acute or serious illnesses in the past.

The menopause occurred in 1929 at the age of 55 years. A sudden hemorrhage, rather profuse, occurred in May, 1943. The patient consulted Dr. Fred B. Nugent of Reading, Pa., and he performed diagnostic curettage at the Reading Hospital in June, 1943, and an intrauterine application of 1,200 mg. hr. of radium was administered. Dr. E. D. Funk, Director of Laboratories, reported the scrapings as follows: "The endometrium is atrophic and consists of a fibrous connective-tissue stroma with a paucity of straight nonsecretory glands. There is no evidence of malignancy. Microscopic diagnosis, atrophic endometrium."

The patient reacted well to this treatment, but continued to have an intermittent bloody vaginal discharge. She also complained of a "bloated feeling" in the abdomen, and had difficulty with urination. External irradiation, or further radium therapy to control the persistent but slight bleeding, was suggested as a therapeutic measure several months later, but discouraged by Dr. G. W. Chamberlain, Roentgenologist at the Reading Hospital, who favored surgical treatment, rather than further irradiation.

*Read at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

Receiving other opinions and advice, the patient eventually consulted the senior author on Feb. 29, 1944. Pelvic examination revealed a multiparous outlet with a moderate cystocele and rectocele. The cervix was atrophic and intact. The fundus, however, was thought to be enlarged, boggy, and in retroflexioversion; the adnexal areas could not be distinguished apart from it When mobilization was attempted, extreme sensitivity was evidenced. A tentative diagnosis of pyometra following irradiation therapy with radium was entertained and surgery recommended if preoperative studies would permit of such a decision.

The advice was accepted and the patient entered Jefferson Hospital on March 6, 1944. She was possibly a substandard risk. Obesity was apparent, her weight being 157 pounds. The vaginal smear (Papanicolaou technique) showed atypical cells, suggestive of fundal carcinoma. The blood count, however, was excellent; urinalysis was negative except for a few leucocytes; bilirubin and bromsulfalein test were normal, as was the blood urea nitrogen, while the urea clearance tests were 38 per cent and 45 per cent on two occasions. The electrocardiogram showed left axis deviation only. Dr. Harold W. Jones, consulting internist, felt that she could undergo major surgery.

Fig. 1.—Section from curettage performed nine months prior to operation showing an atrophic endometrium. Fibrous connective-tissue stroma with a paucity of straight nonsecretory glands. (Hematoxylin and eosin, ×50.)

The findings at operation, March 11, 1944, were most interesting. With continuous spinal anesthesia excellent relaxation was obtained, thus permitting a more certain pelvic examination. This disclosed a relatively small, atrophic uterus that seemed to be displaced anteriorly by a more or less fixed but softened enlargement in the cul-de-sac, apparently originating in the left adnexal region and being adherent to the uterus posteriorly. A diagnosis of hydro- or pyosalpinx, secondary to irradiation endometritis, was then made.

No curettage was performed, the cervix being closed with a figure-of-eight suture after carrying out vaginal antisepsis. The abdomen was now opened by a low midline incision. Few adhesions were encountered, and the pelvis was readily exposed. This revealed what appeared to be a relatively large left pyosalpinx, occupying the cul-de-sac and adherent to a small atrophic uterus, displaced anteriorly. The left ovary was atrophic and adherent, and partial torsion of the tubo-ovarian enlargement was apparent. It was mottled, purplish, and congested in appearance. The right tube was hyperemic and swollen, the right ovary being atrophic and adherent, while the entire right

adnexal enlargement was firmly attached to the posterior layer of the broad ligament and to the infundibulopelvic ligament. There was no gross evidence of peritoneal implants of any sort, and no regional nodal enlargements could be palpated; neither did the liver feel abnormal. The appendix had been removed previously, and postoperative adhesions in this area, as previously noted, were not disturbing.

An operative diagnosis of subacute pelvic inflammatory disease with left pyosalpinx, resultant from previous irradiation therapy with radium, was recorded. No thought of malignancy was entertained. Complete hysterectomy with bilateral salpingo-oophorectomy (Richardson technique) was carried out uneventfully. Eight Gm. of sulfanilamide were placed in the cul-de-sac, and the abdomen closed in routine fashion. No drainage was employed.

Postoperative convalescence was satisfying and uneventful. There was little morbidity, the patient was allowed out of bed within two weeks, and she was discharged from the hospital on March 31, 1944.

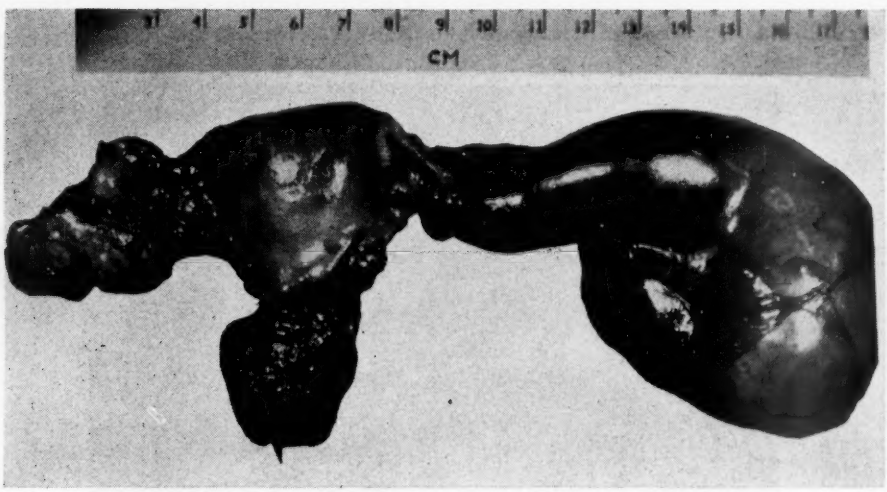

Fig. 2.—Anterior view of removed uterus and adnexa showing sarcoma of left uterine tube and the enlarged right tube. Both ovaries adherent. Uterus atrophic.

The pathologic report, submitted by Doctors Jacob Hoffman, Carl Bucher, and Peter Herbut, was as follows:

Uterus: This consisted of a very small normally shaped organ which measured 6½ by 4 by 3 cm. It was covered by a pink smooth serosa. The uterine cavity measured 4 cm., and was lined by a very thin mucosa. The myometrium measured only 1½ cm. in width. The cervical canal measured 2½ cm. in length, and was lined by a thin, slimy mucosa. The portio measured 2 by 2 by 1½ cm., and was lined by a pink mucosa.

Right tube: This organ measured 8 by ¼ cm. and the distal third was adherent to the ovary. Section revealed a narrow lumen. The serosa was partially covered by adhesions.

Right ovary: This organ measured 3 by 2 by 1 cm. and was very firm in consistency. Section revealed several corpora albicantes.

Left tube: This consisted of a large retort-shaped organ which measured 14 cm. in length. Its diameter varied from ½ cm. in its inner third to 5 cm. at its most distended portions. The middle and outer third was replaced by a cystic tumor which was translucent to light, and was replaced by a gray friable tissue. The fimbria was sealed. The inner third of the organ was distended with blood, and the wall was very thin.

Left ovary: Measured 3 by 2 by 1 cm., and was covered by a rough capsule (wrinkled). Section revealed a homogeneous surface.

Histology.—

Fundus uteri: The endometrium was markedly atrophic and was merely represented by a single layer of low cuboidal epithelium. The myometrium showed a marked increase in fibrous connective tissue and harbored occluded blood vessels. There was evidence of marked senile change.

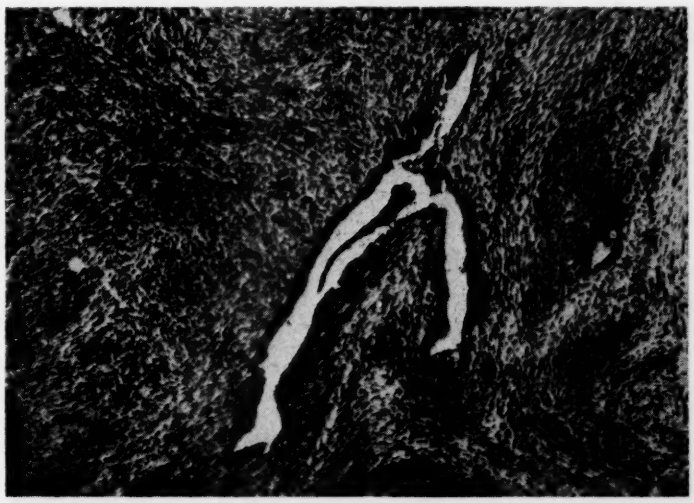

Fig. 3.—Section of the tumor from the left Fallopian tube showing a portion of the tubular epithelium surrounded by sarcomatous tissue. (Hematoxylin and eosin, ×50.)

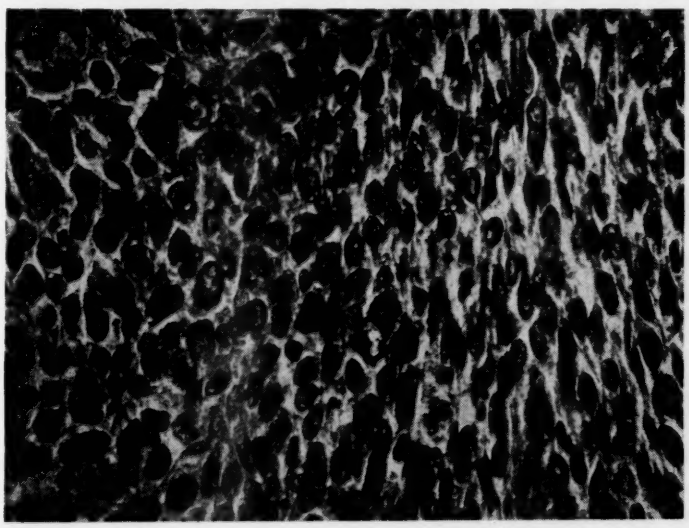

Fig. 4.—Section of the tumor showing intertwining bundles of spindle and round cells. The cytoplasm is moderate in amount and the nuclei are large, deeply stained, but rather uniform. (Hematoxylin and eosin, ×400).

Cervical tissue: The portio was lined by an intact stratified squamous epithelium. The underlying stroma was poorly vascularized and showed an increase in fibrous connective tissue. There was no evidence of malignancy.

Right tube: The lumen was very narrow. The tubal plicae were markedly atrophic. The muscular and serosal coats appeared normal.

Ovaries: Sections revealed several corpora albicans and a poorly vascularized and fibrotic ovarian stroma. There was no evidence of metastatic lesions in either.

Left tube: The distal part of the tube was represented by a dilated lumen, a very thin wall, and atrophic plicae. The inner third was distended with blood and was thin walled.

The middle and outer thirds of the tube were replaced by a tumor growth. This was composed of a very cellular and bizarre growth made up of muscle cells and some fibroblasts. The cells showed a marked disparity in size, and clumping of cells were seen throughout. The tubal architecture was entirely destroyed by this malignant connective tissue growth, of intertwining bundles of spindle and round cells, with giant cells.

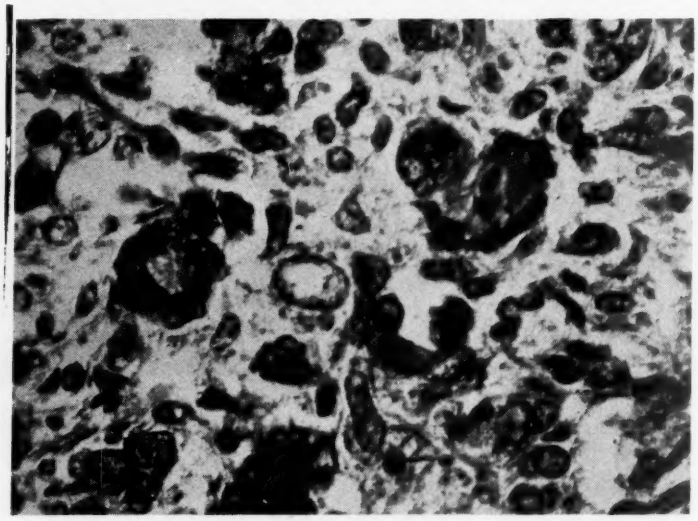

Fig. 5.—Section of the tumor in another area showing extreme pleomorphism with many bizarre single and multinucleated giant cells. (Hematoxylin and eosin, ×400).

Diagnosis.—Atrophic endometrium; senile uterus; normal cervix with senile changes; senile changes of both ovaries; senile changes of right tube; and myosarcoma of left tube.

The final diagnosis was myosarcoma of the left uterine tube, and this was a source of astonishment to me and my associates. Slides were sent to Drs. Robert T. Frank and Emil Novak, who confirmed our diagnosis, and their opinions are quoted herewith.

Dr. Frank: "After careful study of the section, I do not see any other possible interpretation than that of a myosarcoma, as the tumor cells are visible even where they infiltrate normal muscle."

Dr. Novak: "I agree with you entirely as to the pathological diagnosis of sarcoma, an exceedingly rare lesion, as you yourself comment. The growth is apparently of the mixed cell variety, and microscopically shows considerable anaplastic activity in the form of hyperchromatosis, mitosis, etc. In addition there are numerous giant cells, often multinucleated. In a few areas the sarcoma cells are arranged in a definitely perivascular fashion, but this is obviously due simply to the better preservation of the cells around the blood channels."

The patient, now 72 years of age, has been seen at regular intervals since operation, is well and active, presenting no evidence of recurrent disease either upon pelvic or general examination.

Chronological Summary of Previously Recorded Cases

CASE 1.—1886, *Senger:* Aged 59 years, para ?, autopsy specimen. Bilateral tubal round-cell sarcoma with pelvic metastases. Tubal patency not mentioned. Had been admitted to hospital and died in diabetic coma. Gebhard questioned the diagnosis, declaring the specimen to be a carcinoma, but Robert Frank and others have accepted it as a sarcoma.

CASE 2.—1886, *Gottschalk:* Aged 37 years, para iii, operative specimen (salpingectomy?). Right tubal small spindle-cell sarcoma with pelvic and lymphatic metastases. Tubal lumen patent. Death occurred four days post-operatively.

CASE 3.—1889, *Janvrin:* Aged ?, para ?, operative specimen (salpingectomy). Tubal myxosarcoma with embryonal connective tissue and unstriped muscle, whether right or left tube not mentioned. Tubal lumen patent. Death after operation, thought to be due to "general nervous exhaustion in the whole alimentary tract" (adynamic ileus? peritonitis, with intestinal obstruction?).

CASE 4.—1890, *Sänger:* Aged 42 years, nullipara; operative specimen (bilateral salpingectomy and resection of left paraovarian cyst). Bilateral tubal small round-cell sarcoma, with left parovarian cyst in addition. Tubal patency not mentioned. Gebhard questioned this diagnosis also, as did Coe, but other reviewers have accepted it since then. Death occurred eight months later from metastases.

CASES 5 AND 6.—1893, *Jones, C. D.:* In 1890, Prof. H. F. Formad, Coroner's physician of Philadelphia, secured 35 tubal enlargements, supposedly all tubal pregnancies, that were found in women who had died suddenly of intra-abdominal hemorrhage and were autopsied. They were selected from a series of autopsies of over 3,000 adult women, and were submitted to Jones for study. No case histories were available, but three "myelomas of the tube" were described by him—two primary and one probably secondary: (1) large round-cell sarcoma; (2) large spindle-cell sarcoma. (The third was regarded as a secondary melanotic sarcoma.) Tubal patency was not mentioned. He claimed to have traced the gradual transformation of muscle cells into cells of the "myelomata," but this has been disputed. Apart from this interpretation, the illustrations support the microscopic diagnoses of the two primary (and one secondary) tumors, although Von Kahlden and Robert Frank have doubted the acceptance of these cases. Only the primary tumors are recorded in this review.

CASE 7.—1897, *Jacobs* (I): Aged 41 years, para i, operative specimen (bilateral salpingo-oophorectomy and supravaginal hysterectomy). Left tubal myosarcoma. Tubal patency not mentioned. Death occurred one year later.

CASE 8.—1897, *Von Kahlden:* Aged 51 years, para iii, autopsy specimen. Bilateral tubal endothelioma with giant-cell formation, and metastases to both ovaries and peritoneum. Ascites present. Tumor mass protruded through fimbria of right tube. Robert Frank, contrary to other authors, labels the diagnosis as doubtful, which does not seem reasonable in the light of the present review.

CASE 9.—1904, *Jacobs* (II): Aged 27 years, nullipara, operative specimen (bilateral salpingo-oophorectomy and supravaginal hysterectomy). Bilateral tubal spindle-cell sarcoma, with ascites and enlarged sacral lymph nodes. Tubal patency not mentioned. Still alive two months later. No further follow-up noted.

CASE 10.—1909, *Gosset:* Aged 44 years, para iii, operative specimen (bilateral salpingo-oophorectomy and supravaginal hysterectomy). Left tubal perithelioma, with metastatic nodules in omentum and broad ligament. Tubal lumen patent. Right hydrosalpinx. Uneventful convalescence, but no further follow-up.

CASE 11.—1911, *Scheffzeck:* Aged 61 years, para ?, operative specimen (curettage and left salpingectomy (?)). Left tubal spindle-cell and multi-

nucleated giant-cell sarcoma. Tubal lumen patent. Fraenkel questioned the diagnosis, but Robert Frank has accepted it. No follow-up.

CASE 12.—1911, *Barbour and Watson:* Aged 53 years, nullipara (bilateral salpingo-oophorectomy). Left tubal perithelioma with local and generalized metastases and ascites. Tubal lumen not patent. Death occurred eleven days postoperatively.

CASE 13.—1915, *Müller:* Bilateral tubal perithelioma. Whether operative or autopsy specimen not mentioned. A simple statement of fact, presented before the Fifth Congress of Czech Scientists and Physicians, in Prague, 1914, stating that during the previous six years only one such case had been found in the Pith Clinic. No details, as the proceedings of the Congress were apparently never published. It is difficult to accept this case without further evidence than that presented.

CASE 14.—1917, *Bello and Castanedo:* Aged 40 years, para viii, operative specimen (salpingo-oophorectomy and supravaginal hysterectomy). Right tubal round-cell sarcoma. Tubal patency not mentioned. Operative recovery. No follow-up.

CASE 15.—1924, *Bannister:* Aged 45 years, para ?, operative specimen (salpingo-oophorectomy and supravaginal hysterectomy). Left tubal small round-cell sarcoma, associated with multiple uterine myomas, and metastatically involved iliac and aortic lymph node. Tubal lumen filled with tumor tissue. Death seventeen days postoperative, possibly from pulmonary embolism.

CASE 16.—1924, *Dodd* (I): Aged 55 years, nullipara, operative specimen (salpingectomy). Right tubal spindle-cell and "oat-cell" sarcoma. Tubal lumen filled with tumor mass and mucosa destroyed at point of origin. Operative recovery. Well for one year. No further follow-up.

CASE 17.—1924, *Dodd* (II): Aged 60 years, para II, operative specimen (bilateral salpingo-oophorectomy and appendectomy). Right tubal spindle-cell sarcoma. Tubal mucosa smoothed out. Operative recovery. Death from recurrence and metastases two years later.

CASE 18.—1936. *Bride:* Aged 54 years, para i, operative specimen (bilateral salpingo-oophorectomy and complete hysterectomy). Bilateral tubal periendothelioma (perivascular sarcoma). Tubal lumina filled with tumor growth. Operative recovery. No follow-up.

CASE 19.—1938, *Jörgenson:* Aged 62 years, nullipara, operative specimen (salpingectomy). Left tubal giant-cell sarcoma with peritoneal metastases. Tubal patency not mentioned. Postoperative external irradiation. Death forty days postoperative from bronchopneumonia. Autopsy showed no pulmonary metastases.

CASE 20.—1939, *Reiber:* Aged 44 years, para ?, operative specimen (salpingectomy). Right tubal spindle-cell sarcoma. Tubal lumen filled with tumor growth. Operative recovery. Postoperative external irradiation. Well one year later. No further follow-up.

CASE 21.—1945, *Rickford:* Aged 54 years, para iii, operative specimen (salpingo-oophorectomy). Curettage (Aug. 29, 1944) negative. Pelvic operation Mar. 11, 1945. Left tubal spindle-cell sarcoma. Tubal lumen filled with tumor mass, extruding from it and attached to broad ligament and uterus. Operative recovery, with pulmonary infarct sixteen days postoperatively. Postoperative external irradiation. Well seven months later. No further follow-up.

To the above 21 cases designated as sarcomas, is now added the twenty-second case, that of the patient whose case history has been described—a definite myosarcoma of the left uterine tube.

Pathologic Features

Of the 22 cases now referred to, 17 of the specimens were secured by operation and four by autopsy; in one the source was not mentioned.

Seventeen have been described as sarcomas of various types, involving the wall, the mucosa and the lumen. They are subdivided as follows: nine spindle-cell, large and small; four round-cell, large and small; two myosarcoma, one each as giant-cell sarcoma and myxosarcoma, respectively. Of the remaining five, three have been described as peritheliomas, one as endothelioma, and one as periendothelioma. They are included in this series, for although the exact histogenic interpretation is not too clearly understood, and is to some extent controversial, the consensus of opinion of numerous authors seems to be that all of them should be regarded as sarcomatous tumors (Ewing, Boyd, McCallum, Karsner). There is nothing to indicate what actually initiates the development of a tubal sarcoma.

It has been thought better not to include a small group of closely-related tubal malignancies in the listing of reported cases. These consist of: (1) Seven malignant mixed tumors classified in general as "carcinosarcomas," with certain histologic modifications in two of them. (von Franque, Sänger, Schafer, H. R. Spencer, Amann, Motta, Leuret.) (2) A case described as a "mesothelioma" (Egglington) and one spoken of as a "coelomic mesothelioma" (Collilas and Masciottra). Because of their histologic similarity to true epithelium, these lesions are probably better classified as carcinomas.

The above compilation of the 22 cases now reported provides interesting comment. As noted, seven of the 21 previously reported cases have been subjected to criticism by others.

Thus Gebhard questioned both the cases of Senger and Sänger, but this is not surprising in view of the fact that these cases, together with those of Gottschalk and Janvrin, were the first tubal sarcomas to be recorded. Naturally, their interpretation would be subject to minute criticism as new pathologic entities. Dietrich regarded the lesion as a mixed one—sarcoma and carcinoma.

The cases reported by Jones may have been doubted by Von Kahlden, and more recently by Robert Frank, perhaps because of the bizarre theory of tumor development that Jones stressed, rather than upon the histologic picture presented. Our feeling, however, based on a careful perusal of the original article and its illustrations, is that these cases are entitled to inclusion in the series. Our opinion is the same with respect to Von Kahlden's case, accepted by all reviewers with the possible exception of Robert Frank.

Fraenkel disputed Scheffzeck's case on the basis of a comparative study with a certain group of tubal carcinomas of his own, in which he pointed out distinct histologic similarity between them, but Robert Frank and others include the case in reviews of the subject.

With respect to Müller's case, our estimate is that the recorded reference is too brief for certain analysis, but that it should be mentioned in the series as a reported instance of tubal sarcoma.

The case presented herewith adds a sixth to those emanating from the United States—all but one having been encountered in Philadelphia. Of the remaining 16, one appeared in Peru, S. A., and the remainder in continental Europe and the British Isles.

Clinical Features

Age Incidence: The age incidence in this series coincides closely with that of the fundal carcinoma group, all but two of the patients ranging in age from 40 to 70 years. The youngest were 27 and 37 years of age, respectively; the eldest (our patient) being 70 years. This is also similar to the age incidence in tubal carcinoma.

Symptomatology.—A critical review of the symptoms exhibited by the patients in the series collected shows that the manifestations of tubal sarcoma mimic those described in carcinoma of the tube, the commoner malignant lesion. This is easily understood when the lesions described are viewed in the light of the histologic picture presented, for it has been shown that controversies have repeatedly arisen with respect to the microscopic diagnosis and its similarity to epithelial malignancy. Unfortunately, not all of the histories reviewed are well detailed.

Practically all of the patients were in the premenopausal or postmenopausal epochs. Among the former, menorrhagia and/or metrorrhagia were mentioned, and not infrequently an abnormal vaginal discharge in addition, either serosanguineous or semipurulent. In the postmenopausal group, the discharge was generally described as bloody, but was occasionally of a profuse, watery nature. In the two younger patients (27 and 37 years of age) the menses were normal.

In nearly every case, pain was a prominent symptom. This varied in intensity and duration, being distinctly pelvic in some, diffusely abdominal in others. Often pain went hand-in-hand with gastrointestinal symptoms, such as nausea and diarrhea, together with abnormal bleeding and discharge. Abdominal distention, the sensation of having an abdominal enlargement, pronounced malaise, loss of weight, and even emaciation were sequential to a late advancing lesion with extension or metastases, a train of symptoms observed in about one-third of the patients.

Symptoms such as those recounted may be encountered in any type of adnexal malignancy, either tubal or ovarian, except that the latter may also occur in women of a relatively younger age group.

Pelvic Examination and Diagnosis.—Abdominal and pelvic findings varied with the extent of disease present. Abdominal distention or enlargement were noted in five patients, emaciation or cachexia in eight. In most instances pelvic enlargements were discernible, amounting in several instances to a so-called "frozen pelvis." Comparative descriptions varied in size from a "walnut" to a "grapefruit."

In no case was the diagnosis of tubal malignancy entertained preoperatively. Actually, a preoperative diagnosis of any sort was mentioned but 10 times among the 17 operative cases. The diagnoses prior to operation were:

ovarian carcinoma, two; pelvic inflammatory disease, two; ovarian cyst and pelvic inflammatory disease, one; uterine fibroids, two; tuberculosis, one; "enlargement springing from uterus," one; pyosalpinx or hydrosalpinx following intrauterine irradiation (our case).

Operative and Autopsy Findings.—Bilateral tumors were reported in six cases; left-sided in eight, right-sided in five. In three the site was not mentioned. Patency of the tubal lumen was observed six times, is not mentioned in nine cases, while in the remainder the growth extended to, and filled the tubal lumen with extrusion from the fimbriated extremity in some instances. The diameter of the tubal enlargements varied in general from 2 to 20 cm. The appearance was equally variable, depending upon the extent of the lesion and its environment. Usually the tube or tubes involved were distended, of varying shape and consistency, being either solid, soft, cystic, or at times papillary. No predominant coloring was noted, but whenever extrusion of the tumor mass was mentioned, it was described sometimes as being "white and brain-like" in appearance, or "cauliflower-like." Adhesions and/or metastatic growths were present in the majority of cases. Accompanying lesions of adjacent pelvic organs were relatively infrequent.

Treatment.—The operative procedures in 17 patients were: salpingo-oophorectomy or salpingectomy, either unilateral or bilateral, 10; with accompanying supravaginal hysterectomy, 5; with complete abdominal hysterectomy, 2 (including our case). In one instance a negative curettage had been carried out seven months before the abdominal operation was performed; in our case, nine months before, with intrauterine radium as well. Postoperative x-ray was employed twice in recent years (1938-1939).

Results: Nine operative recoveries, of whom four were living and well two to twelve months after operation, when the cases were reported; one has survived for two years, and is apparently well and free of recurrence (our patient). No follow-up record is noted in the remaining four reported operative recoveries.

Five postoperative deaths occurred (four to forty days); three remote deaths occurred from metastases.

Four of the cases in the series, as noted, were autopsy reports (Senger, Von Kahlden, Jones[2]). Whether it was an autopsy or operative specimen is not mentioned in one case (Müller).

Summary and Discussion

Our reasons for presenting this communication are twofold. First, to record an unusual pathologic entity, and to review the literature to date with respect to it; second, to discuss the symptomatology, physical findings, and the difficulties encountered in arriving at an accurate preoperative diagnosis.

The first objective has been accomplished, as noted.

With respect to the second, it has been seen that the symptomatology is no wise distinctive, but is akin to that of tubal carcinoma or to ovarian carcinoma in some forms.

As stated by Anspach before this Society in 1930, and by others as well, malignancy of the tube is more likely to occur in the late reproductive, menopausal, or postmenopausal periods of life. Vaginal bleeding is not nearly as well-marked as in uterine carcinoma; this symptom is much more likely to be in the nature of a watery, blood-tinged discharge. Pain is probably the most constant and conspicuous symptom, often associated with gastrointestinal annoyance.

The physical signs may be regarded as early and late. In the former, the presence of an adnexal mass (or masses) is about all that one can expect to find. With the advance of the lesion, abdominal distention, ascites, and an extensive pelvic mass are found naturally, while emaciation and cachexia accompany these.

Taking into account the symptoms and signs as mentioned, it is obvious that certain truths evolve with respect to diagnosis. Knowing the clinical manifestations to be what they are, early diagnosis, as in malignancy elsewhere, is the goal to be aimed at. The popularity of diagnostic curettage affords ample opportunity to think of tubal carcinoma or sarcoma when the procedure is negative and especially in the presence of adnexal enlargement. In one of the recorded cases, curettage was negative seven months prior to the laparotomy that disclosed an extending tubal sarcoma. In our own case, curettage and a radium application preceded operation by nine months, due to no fault of the primary operator who advised prompt retreatment. In one of the other cases there had been a curettage immediately preceding the laparotomy.

The physical status of the patient often determines the ease of detecting pelvic pathology. In the lean person, it is not nearly as difficult to carefully follow the patient in whom a tubal lesion is thought of or suspected as it is in the obese individual. Hence, in the latter, examination under anesthesia, with preparations made for immediate abdominal operation if a definite adnexal mass is found, is the procedure of choice.

Once operation is decided upon, the procedure should be complete abdominal hysterectomy with bilateral salpingo-oophorectomy, rather than simple removal of the affected tube and/or ovary. Of course this is not always possible, as has been learned from the cases reviewed. Postoperative irradiation therapy is indicated when operation has been incomplete, either intentionally or of necessity, and the diagnosis of malignancy has been made in the laboratory; likewise when metastases are observed. The question of irradiation therapy when operation has been complete, and where no metastases are visible, is debatable. A large proportion of the recorded cases that were operated upon occurred in the days when x-ray therapy was unknown or in its infancy, and criticism from that source is unjustified. It should be apparent, too, that the gross differentiation between sarcoma and carcinoma of the tube is impossible; in fact a benign lesion of the tube might well be diagnosed visually, as happened in our case.

Finally, it is evident that the prognosis of tubal sarcoma, as well as tubal carcinoma, is doubtful at best. Curability can only be enhanced by early diag-

nosis and prompt treatment. The latter, in the final analysis, can be made possible only by a keen appreciation of the symptoms and findings that have been stressed, but more probably by the periodical pelvic examination of women through continued lay and professional education.

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Discussion

DR. GEORGE H. GARDNER, Chicago, Ill.—First, including the case which Dr. Scheffey has reported, there are 22 more or less authentic instances of primary sarcoma of the Fallopian tube recorded in the world's literature. In other words, only 4 per cent of all malignant tumors of the tubes are sarcomas. Despite their rarity, I shall be much surprised if someone does not report an additional case very soon.

Second, Dr. Scheffey has failed to comment on the mechanism of the postmenopausal bleeding which brought his patient to her physician. I hope he will elucidate. Was it

an escape of blood from the tube into the uterus? That is the probable explanation, but a most unusual phenomenon.

Third, as time goes on, all of us use intrauterine radium less frequently as a panacea in the treatment of inadequately explained postmenopausal bleeding. Dr. Scheffey's patient is a case in point. Her clinical picture was obscured, in part at least because she had been given radium; and surgery was long delayed because it was thought that her symptoms were the result of local reaction, or infection, incident to the intrauterine radium irradiation.

DR. SCHEFFEY (Closing).—With regard to Dr. Gardner's question as to the primary symptom in this patient, it was apparently a minor hemorrhage. I do not know about the actual amount of blood lost, but it was sufficient to cause her to go to her physician who very rightly performed a diagnostic curettage and applied radium as seemed indicated. It was no fault of his that the patient did not have re-treatment sooner, for she demurred for some time thereafter and sought various opinions.

I would like to emphasize again that it is in the case of the stout patient in whom menopausal and postmenopausal bleeding occurs that we are prone to rely often on diagnostic curettage and a radium application, instead of being prepared to perform abdominal section.

SOME CLINICAL ASPECTS OF THE Rh FACTOR IN OBSTETRICS*

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THE discovery of the Rh factor is a recent one, it having been first detected by Landsteiner and Wiener[1] in 1940. Levine and Stetson[2] and others had previously suspected the presence of some such substance in the blood. So great is the importance of this factor, both scientifically and clinically, that a voluminous literature has developed. It is impossible to review, in this presentation, the hundreds of papers that have been written. Furthermore, the serologic ramifications are so perplexing that it is best to avoid the controversial aspects of the subject and to confine ourselves to a consideration of the clinical implications.

However, a brief review of the fundamental principles is necessary. It is known that the Rh factor is not a single entity, but a complex one, which helps to explain some of the varying clinical manifestations. Wiener and others have shown that about 85 per cent of white people are Rh positive, with a much greater proportion in other races (Table I from Levine).

Of the 15 per cent negative individuals in the white race, we would expect less than half to be females of the childbearing age. However, Halperin, Jacobi, and Dubin[3] found 66 Rh-negative women in 500 consecutive determinations in pregnant patients (13.2 per cent). Levine, Katzin, and Burnham[4] state that in about 9 to 10 per cent of marriages in the white race, there is the union of an Rh-negative woman and an Rh-positive man.

It is generally thought that in about only 5 per cent of such unions will the baby be affected, and this complication is very rarely seen in the first pregnancy. Buxton and McDuff[5] found 66 cases of erythroblastosis fetalis in 28,898 deliveries, an incidence of 1 to 516. Javert[6] gives a figure of 1 in 438, while Wolf and Negus[7] found their ratio to be 1 in 568. Thus, we can expect an affected infant in about 1 to 500 deliveries. Levine and Waller[8] state that 1 in 150 to 200 newborn children have erythroblastosis, but that about only one in 438 develop clinical manifestations of the disease.

The chief point of clinical interest is this occasional delivery of an infant in whom erythroblastosis fetalis is already present or develops shortly after birth. Wiener[9] proposes the more appropriate designation of "hemolytic disease of the newborn." This occurs in three forms, the anemic, the icteric, and the hydropic types. The mortality is about 55 to 60 per cent, the prognosis being gravest in the hydrops type, and best in the anemic type. Of great clinical importance also is the occasional transfusion reaction following the administration of Rh-positive blood to an Rh-negative recipient, noted more particularly in the last of a series of repeated transfusions.

In approximately 90 per cent of all cases of hemolytic disease of the newborn the mother is Rh negative and the father and the infant are Rh positive.

*Read at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

TABLE I.

RACE	NUMBER TESTED	PER CENT POSITIVE REACTIONS	PER CENT NEGATIVE REACTIONS	INCIDENCE OF ERYTHROBLASTOSIS FETALIS (PER CENT)
White	334	85.0	15.0	2.1
Negro	264	95.5	4.5	0.7
Chinese	150	99.3	0.7	Very rare
Japanese	150	98.0	2.0	Very rare

The small group of 10 per cent will be considered later. The disease rarely manifests itself in the first pregnancy, and, when it does, there is practically always a history of one or more transfusions, the donor or donors being known to be Rh positive, or presumed to be so. Rh testing before transfusion is of course a new development, and with 85 per cent of our white population being in the Rh-positive group, the Rh-negative person being transfused has had only a slight chance of receiving Rh-negative blood. Levine[10] believes that, where hemolytic disease of the newborn is found in the first infant of an Rh-negative woman who has never been transfused, the intramuscular injection of blood to the mother in infancy or in early childhood may have initiated the iso-immunization.

The course of events appears to be as follows: The Rh-positive blood of the fetus (the factor is in the red cells) in some manner crosses the placental barrier. Of course, it has been known for years that fragments of the villi break off and are transported by the maternal blood stream to various parts of the mother's body, particularly the lungs.

Levine[8] believes that these slight lesions might suffice for the entrance of fetal blood into the maternal blood stream, or that other microscopic solutions of continuity might occur. He estimates that only 0.13 c.c. of Rh-positive fetal blood is needed to produce iso-immunization in the Rh-negative mother. Once this occurs, anti-Rh agglutinins are formed, which pass back across the placental barrier to the fetus, produce destruction of the Rh-positive red cells (carrying the Rh factor), with consequent overstimulation of the hemopoietic organs, and a resultant outpouring of immature red cells.

This process is a slow one, so that it can be stated that the first born child of an Rh-negative woman and an Rh-positive man is almost never affected in this manner. The second one usually manifests hemolytic disease of varying intensity, but at times this does not develop until the third or even a later pregnancy. The fetus, as a rule, is not affected until late in pregnancy. It may die in the uterus days or weeks before delivery, or may die even after birth, or may recover if the disease is not of too severe a type and proper treatment is instituted at once. Rarely is abortion caused, as the titer of antibodies in the maternal blood is usually rather low early in pregnancy, and tends to rise as gestation advances. Once the state of iso-immunization is produced, it appears to persist for the lifetime of the woman (Levine[11]).

Iso-immunization of the Rh-negative woman has also been produced many times by the transfusion of Rh-positive blood, especially if repeated.

In a study of 700 Rh-negative women pregnant for the first time, Moller, Levine and Yarrow[12] found 28 cases of hemolytic disease of the newborn. In

19 of these, there was a history of one or more transfusions of the mother, the intervals being as great as eight to ten years. It was possible to check some of the donors, and all were found to be Rh positive. In these patients, the iso-immunization was particularly pronounced; the child was mildly affected in only one case, six were seriously ill, and fetal death occurred twelve times. In the other nine patients (with no history of transfusion), the disease was much milder. There was only one fetal death. Levine and Waller[8] feel that the immunization of these mothers might have been caused by the intramuscular injection of blood years before. We have studied two patients (one in the senior author's practice) who were iso-immunized by transfusion four and nine years, respectively, before the first pregnancies. One delivered a still-born baby, and has since lost a second child (Case 1*). In the other case, the first infant died forty-eight hours after delivery. She has subsequently lost a second baby, dead ir utero (Case 2).

As stated above, 90 to 92 per cent of infants with hemolytic disease are born to Rh-negative women with Rh-positive husbands. The others may be due to iso-immunization due to Rh subtypes, or to the A, O, and B blood factors, or to the very rare Hr factor. A case illustrative of the first possibility was reported by Moller, Levine, and Yarrow.[12] The mother was Rh positive, subtype Rh_2, while the father and the infant were Rh positive, subtype Rh_1. Wiener[21] reports an instance in which the mother was Rh positive, subtype Rh^1; the father and the infant were Rh positive, subtype Rh_1, Rh_2. Polayes[13] reports two cases which seemed to be due to iso-immunization of the mothers with the A antigen of the babies. Tilden and Chang[14], from Hawaii, report an infant with hemolytic disease, with both parents Rh positive and no iso-agglutinins found in the mother's blood after delivery. In three of four other cases observed by the authors, both parents were Rh positive. These could probably be explained on the basis of the Rh subtypes. Davenport (junior author) has studied a case in which the mother was Rh positive, subtype Rh^1, and the father and the affected infant were Rh_1. The iso-immunization was apparently caused by transfusion from the husband after the second delivery (no reaction). A second transfusion at this time was also free from reaction (another donor), but a third transfusion from a third donor was followed by a chill and fever. In the next pregnancy (1945) the infant showed a mild erythroblastotic anemia with slight jaundice two days after delivery. The baby recovered without transfusion. In another case of Davenport, the erythroblastosis (second child) was apparently due to incompatibility of major blood groups between husband and wife. The father and the baby were Rh positive, Group B, and mother was Rh positive, Group O. There was no evidence of anti-Rh or anti-Hr antibodies. However, her anti-A titer was 1:128 (normal limits) while her anti-B titer was 1:2048, so that there was a very definite specific increase in the latter titer.

Diamond[15] states that "Erythroblastosis fetalis may develop in infants who do not have hemolytic anemia due to Rh incompatibility, especially those with infection, with congenital malformation of the heart, with anoxia due to atelectasis of the lungs and with intracranial hemorrhage, and even extremely premature infants." Finally, as mentioned by Levine, and Waller[8] in some of these infants there is reason to believe that the diagnosis was erroneous.

From the clinical point of view, it seems that it is wise to test all obstetric patients for the Rh factor, particularly as the possibility of transfusion is always present. The use of what is known as the 85 per cent serum seems to be the practical procedure, reserving the search for the rare subtypes for special cases, and this can be done only by those serologists to whom these particular

*Details at end of article.

testing sera are available. If the wife is found to be Rh negative, it is proper to test the husband also. In this small series of cases (122) under the care of the senior author, it is interesting to note that in four instances the husband was found to be Rh negative also. Of these, three women were multiparas, and, of course, the children already born were found to be Rh negative as well. The fourth woman is a primipara not yet delivered. Hence, there was no possibility of iso-immunization in the present pregnancy. In another multipara the wife was positive and the husband negative. A healthy child was delivered. In the Rh-negative primigravidas with no history of previous transfusion there is no cause for worry, but tests for antibodies are proper, unless we can rule out the possibility of the intramuscular injection of blood in the infancy of these mothers. In the multigravida, tests for agglutinins and blocking antibodies are necessary, and these should be repeated at intervals during the pregnancy, and the titer should be determined when antibodies are found. Wiener's[16] conglutination test should also be routinely employed in the test for Rh antibodies, and we have so used it since its discovery in 1945.

In this connection, it must be noted that investigators were puzzled by finding that anti-Rh antibodies were not detected in as high a percentage of established cases of erythroblastosis fetalis as was expected. This was clarified by the discovery by Wiener[17] of what he calls the blocking antibody, which was also discovered independently by Race and Taylor[18] and named by them the incomplete antibody. Wiener described this as follows: "In addition to the Rh antibodies that produce hemagglutination there are others able to combine specifically with Rh positive cells without producing a visible reaction. If Rh positive blood is mixed with serum containing antibodies of the other type, the blood is not agglutinated by anti Rh agglutinating sera, presumably because all the combining sites on the erythrocytes have been occupied. This type is called the blocking antibody." Hence, testing for these antibodies is also essential in the study of the Rh-negative pregnant woman, especially if she is a multipara, unless the husband is also Rh negative. It appears to us that the presence of the blocking antibody gives a graver prognosis than the presence of agglutinins alone.

Fortunately, it happens that about 50 per cent (49 per cent, Levine) of the Rh-positive husbands of these Rh-negative women are heterozygous. If he should be so in a given instance, there is a 50 per cent chance that the fetus will be Rh negative, and hence will not be affected. However, the husband's status cannot be determined, except by testing with the very rare anti Hr serum, which is not available for routine use. Therefore, we have to draw upon the clinical history for aid in determining this point. Naturally, the history will not aid us unless there have been several pregnancies. This information has been available in only two of our cases (Cases 3 and 4).

As stated above, 122 patients from the senior author's practice are reported here (Table I). Of these, 47 were primigravida, of whom 40 were Rh positive and seven were Rh negative. Of these Rh-negative women, one has been delivered of a healthy normal baby, and six are undelivered. Seventy-five were

TABLE II.

	DELIVERED	UNDELIVERED
Primigravida		
Positive	4 (1 misc.)	36
Negative	1	6
Multigravida	13	46
Positive	7	9
Negative	25	97

multigravidas, of whom 59 were Rh positive and 16 were Rh negative. Of these Rh negative, seven have been delivered, and nine are still undelivered. Three of the Rh negative women have delivered erythroblastotic infants. Mrs. F.'s first child was healthy, the second died in utero several days before delivery; erythroblastosis was seen at autopsy (case 5). Mrs. V.'s (Case 3) fifth child died in utero two days before delivery. She has since had a healthy child, and is now pregnant again, with no agglutinins or blocking antibodies in her blood on March 1, 1946. However, on May 20, 1946 (Case 3), antibodies were found so that prognosis for the present pregnancy is not very good. Mrs. DeB. (Case 1) was evidently iso-immunized by repeated transfusions in 1940; her first child died in utero (erythroblastosis at autopsy), and her second died of erythroblastosis three days after section at the eighth month. Of the four Rh-negative multiparas with Rh-negative husbands, two have delivered normal healthy children, and two are undelivered.

In these 122 cases, the percentage of positive and negative cases does not, of course, represent the true proportions that would be found in a large consecutive series. Besides the patients commented on above, we have selected others not included in this series of 122 for special consideration. These will be referred to later.

It might be mentioned that the majority of these tests were made by most excellent clinical pathologists. The Rh-negative patients were retested by the junior author, and, of these, five were found to be Rh positive, and are listed as such. It is hard to explain this discrepancy, unless it be on the basis of difference of sera, or delay in testing, or difference in potency of the sera. We might also note that, once in this series and once in another case, false positives were obtained due to bacterial contamination of the testing sera or to a technical error. Hence, meticulous attention to details is essential. It is also essential for accuracy to use at least two sera of the same specificity but of different lots, both of which should be frequently tested against Rh-positive and Rh-negative control bloods. As Levine[21] points out, the human testing sera are preferred to the experimental sera secured from laboratory animals.

Case Reports

CASE 1.—Mrs. DeB. had had an operation for ruptured appendix in 1940, and was transfused. Donor not available at present for checking. Delivery of stillborn macerated child (first pregnancy) in 1944. Reported Rh positive (error) in January, 1945. Pregnant in April, 1945. Found to be Rh negative and iso-immunized. Husband found to be Rh positive. Section was performed one month before estimated date of confinement. Baby was living, weighed 5 pounds, developed icteric type, and died in three days.

CASE 2.—Mrs. E. H., aged 21 years, was transfused at 12 years of age; uncle was donor, Group A, Rh positive. No reaction. First pregnancy terminated Aug. 29, 1944. Infant markedly jaundiced, died two days later. Autopsy: typical findings of erythroblastosis of the spleen and liver. Mother, Group A, Rh negative, husband Group A, Rh positive. In second pregnancy mother found to be iso-immunized with blocking antibody present. Baby died in uterus before delivery.

CASE 3.—Mrs. V., Rh negative; Mr. V., Rh positive.

First baby, 1930; premature, 6 pounds; living, Rh positive, jaundiced at birth.

Second pregnancy, 1932; miscarriage at three and one-half months.

Third pregnancy, 1934; premature, infant, at seven and one-half months, weighing 4 pounds. Baby lived five days. Cause of death not known.

Fourth pregnancy, 1936; term pregnancy, baby weighing five and three-quarter pounds, two transfusions received from father. Child is living, and is Rh negative.

Fifth pregnancy, 1941; term delivery. Intrauterine death two or three days before delivery. No autopsy.

Sixth pregnancy, 1942; baby was slightly premature, weighed five and one-quarter pounds, had no jaundice. Child is living, and is Rh negative.

Seventh pregnancy; due September, 1946. On March 12, 1946, the mother's serum showed no antibodies. On May 22, 1946, conglutination test was positive 1:128, blocking test positive, 1:64. Prognosis for successful outcome of this pregnancy was not so favorable. Section was performed at eight months. Baby survived.

Husband is heterozygous (Rh Rh).

CASE 4.—Mrs. R. D. C. Her first pregnancy occurred in 1940, and ended in a miscarriage at two months. A normal child was born in June, 1941. During next pregnancy her basal metabolism rate was +11, last menstrual period was June 8, 1945. Delivered March 15, 1946 of a healthy girl. Husband, Rh positive; first child, Rh negative, wife Rh negative. No evidence of iso-immunization. Husband is hence heterozygous.

CASE 5.—Mrs. F. was never transfused. Her first child was born in 1942 at term, healthy. Second child was born in 1944 at term; had been dead in utero four days. Autopsy: erythroblastosis. Patient, Rh negative; husband Rh, positive; son, Rh positive. One year later patient's sera still contained blocking antibody and agglutinins.

CASE 6.—Mrs. O. H. In 1943 and 1944 she had term deliveries, resulting in normal children. In 1945 she had a term delivery with a living child. At ten days, the baby became pale and slightly icteric. It was transfused with Rh-negative blood, and lived. Husband is Rh positive; three children are Rh positive; wife is Rh negative. Serum shows anti Rh agglutinins and blocking antibody. Husband is probably homozygous. Will next baby survive?

CASE 7.—Mrs. H. F. experienced three miscarriages at three months; then one at five months; then a full-term normal child, now four years old; then two more miscarriages at three and one-half months. Operated upon for tubal pregnancy in 1938. During next pregnancy her basal metabolism rate was + 22. Last menstrual period had been Dec. 3, 1944. Mrs. F., Rh negative; husband and child, Rh positive. No agglutinins or blocking antibody on May 8, 1945, and on Aug. 2, 1945. Premature delivery of twins occurred Aug. 5, 1945, both lived. Rh factor did not affect pregnancy.

CASE 8.—Mrs. L. F. Miscarriage occurred at six months in 1942. History of hypothyroidism. No history of blood transfusion. Rh type of first husband not known. Remarried in October, 1944. During next pregnancy her last menstrual period occurred Oct. 4, 1945. Wife, Rh negative; husband Rh negative. Rh factor no complication of her pregnancy. She was taking 2 grains desiccated thyroid daily. A term delivery with a normal child resulted.

CASE 9.—Mrs. J. P. E. Jr. Patient was never transfused. First child, three years old. Second delivery, February, 1946 resulted in a healthy child. Husband, wife, and first child all Rh negative, no sensitization possible.

CASE 10.—M. R., a Negro woman, had a term delivery in 1944, resulting in a normal child. Patient was transfused from bank blood. In 1946, delivery of an erythroblastosis (hydropic) child, died at birth. Husband, Rh positive; first child, Rh positive; mother, Rh negative. Mother's blood showed agglutinins and blocking antibodies present. Husband probably homozygous.

CASE 11.—Mrs. A. R. In 1943 a miscarriage occurred at three and one-half months. She was transfused from husband, and experienced urticarial reaction. In 1944, premature delivery of a six and one-half-month fetus occurred, which was grossly normal. No autopsy. In 1945, the patient had a miscarriage at two and one-half months. Tested one month later, husband was Group O, Rh positive; wife was Group O, Rh negative. Iso-agglutinins and blocking antibodies were present. Prognosis for future pregnancy is not good.

CASE 12.—Mrs. S., aged 30 years, had miscarriages in 1937 and 1938. A term delivery occurred in September, 1941, resulting in a normal child. Second delivery was January, 1946; the baby lived three days. Clinical diagnosis was erythroblastosis. No autopsy. In May, 1946, the father was found to be Group O, Rh positive; son, Group B, Rh positive; mother, Group B, Rh negative. Congultination and blocking test was positive. Prognosis for future pregnancies is very grave.

Comments

Case of Mrs. DeB. (Case 1). It is very doubtful that this patient will ever be able to have a healthy child, unless by artificial insemination from an Rh-negative donor.

Mrs. E. H. (Case 2). Same comments as in previous case.

Mrs. V. (Case 3). It is probable that this patient can have more healthy children as the husband is heterozygous.

Mrs. R. D. C. (Case 4). We have not yet been able to obtain blood from the second child for a study. If it is negative, the prognosis for next pregnancy is excellent. If it should be positive, there is a possibility of iso-immunization, and the mother's blood should be tested frequently for antibodies.

Mrs. F. (Case 5). The fact that this patient's blood still contains antibodies at the end of a year makes the prognosis for future pregnancies very guarded. It is interesting to note that she is a double first cousin of another Rh-negative woman in this series. This second patient, however was fortunate enough to have married an Rh-negative man, and to have had healthy children. Extensive studies on the parents and siblings of these patients are to be undertaken.

Mrs. O. H. (Case 6). In view of the fact that all three children are Rh positive, it is most probable that the husband is homozygous, and therefore it is probable that succeeding children will be affected with hemolytic disease with increasing severity.

Mrs. H. F. (Case 7). Tests have not been performed on the twins delivered Aug. 5, 1945. This is to be done, as it will help us to determine whether the father is homozygous or heterozygous.

Mrs. M. R. (Case 10). This is the only case of hemolytic disease due to Rh incompatibility found in the Negro, as is to be expected because of the rarity of Rh-negative women in that race. She may have been sensitized by the transfusion or by the previous pregnancy, or by both. Another case has been encountered by the junior author, but it was strongly suspected that this patient has white blood, so she was not included in this study.

Mrs. A. R. (Case 11). The fact that antibodies were found in the patient's blood a month after an early miscarriage makes the prognosis for future pregnancies very unfavorable.

Mrs. S. (Case 12). In this patient, also, antibodies were found four months after delivery of an affected child. Consequently, we also consider the chance of a healthy child in a future pregnancy is not good.

Although this question is more in the province of pediatrics, a few words as to management of Rh-negative patients might be in order. As far as is known, little can be done to prevent sensitization by pregnancy. However, sensitization

by transfusion can be avoided, as emphasized repeatedly by Levine, by being certain to transfuse Rh-negative females of whatever age only with compatible Rh-negative blood. Furthermore, it appears that at present nothing can be done to eradicate such sensitization of an Rh-negative woman once it has been established. The termination of pregnancy at seven and one-half or eight months by induction or by cesarean section has been advocated, and successful cases have been reported by Diamond.[15] Immediately after delivery the baby should be transfused with compatible Rh-negative blood. Darrow[19] feels that Rh-positive blood can be used for these infants, but the general opinion is that this is not wise, as the agglutinins present in the baby's serum would probably destroy the transfused Rh-positive cells. As mentioned above, the prognosis for these babies is not very good.

Conclusions

1. Tests for the Rh factor, as soon as facilities, trained workers, and proper sera are available, should be carried out on all pregnant women.

2. In Rh-negative women, the husbands should be tested also. If the husband is negative, the fetus is bound to be negative, and will not have hemolytic disease of the newborn.

3. In Rh-negative women with Rh-positive husbands, tests for Rh antibodies should be performed. This is imperative in multigravidas and in primigravidas with history of previous transfusion. If none is found on repeated tests, the prognosis for the fetus is good.

4. If antibodies are found, the titer should be determined at frequent intervals during the pregnancy.

5. If the titer is rising as the pregnancy progresses, induction of labor or cesarean section at seven and one-half or eight months might enhance the baby's chances. This question is still in doubt.

6. After delivery, the erythroblastotic infant should be transfused at once (the veins of the umbilical cord can be used) with Rh-negative blood, and this should be repeated as often as indicated.

7. The chances of securing a healthy child in subsequent pregnancies when one or more erythroblastotic children have been delivered is not good, unless the husband be proved to be heterozygous. Then it is about 50 per cent.

8. If the husband is homozygous, the next pregnancy should not occur until several years have elapsed after repeated negative tests for antibodies. Even then, the risk is great, as the reticulo-endothelial system probably retains the sensitization for life.

9. Artificial insemination, as suggested by Potter and Willson[20] and by Levine,[22] might be performed, with due regard for all moral and legal implications.

10. It is imperative that all Rh-negative females requiring transfusion, whatever age, receive only compatible Rh-negative blood.

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(For Discussion, see p. 932.)

REVIEW OF CASES OF Rh ISO-IMMUNIZATION DURING THE PAST FIVE YEARS IN THE ROYAL VICTORIA MONTREAL MATERNITY HOSPITAL*†

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SINCE the discovery of the Rh factor,[1] extensive investigations have been carried out by many workers. It has been demonstrated that the Rh factors play a role in the pathogenesis of hemolytic disease of the newborn[2, 3] and in intragroup transfusion reactions.[4] A review of this work is beyond the scope of this paper. For a comprehensive background of the subject, the reader is urged to refer to the excellent recent publications by some of the outstanding authorities in this field of research.[5-8]

Opportunities for the thorough study of Rh iso-immunization as a cause of hemolytic disease of the newborn have been limited by the relative infrequency of this disease. In addition, much has been missed in explaining the mechanism of the disease and its antepartum prognosis because of the existence of two types of Rh antibodies, one of which was demonstrated only recently. These antibodies have been variously named by different authors,[7, 9-11] but we persist in using the terms "agglutinating" and "blocking" antibodies. Most cases are still available for postpartum study and, if these be investigated both from the maternal and fetal point of view, much useful information may be obtained.

It is with such a study that this paper is concerned, namely, a review of the obstetric cases delivered at the Royal Victoria Montreal Maternity Hospital for the five-year period ending Dec. 31, 1945—a total of 12,114 cases. The hospital files for (a) "fetal deaths," (b) "fetal complications discharged alive" and (c) "neonatal blood transfusions," were examined for cases of erythroblastosis, severe jaundice of the newborn, severe anemia of the newborn, hydrops, hemolytic anemia of the newborn, or any other diagnosis which might have been classified under hemolytic disease of the newborn.[12] A total of 37 cases was found, giving us an incidence of clinical diagnosis of hemolytic disease of the newborn in one out of every 327 deliveries.

The relevant information from the case records of these 37 cases was compiled. Home visits were made in all cases which could be traced with the object of examining the child if still alive, checking histories, and obtaining blood from all available members of the family. In those cases where the child survived, it was subjected to a cursory examination to ascertain whether it could be classified in the broad group of normals, or whether it was an obvious subnormal, either physically or mentally. With the blood obtained, the A.B. and

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O. and Rh types were determined, and Rh or A.B. and O. incompatibility established. The mother's serum was further tested for evidence of iso-immunization.

For Rh typing[13] standard Rh_0 sera obtained from various sources were used. To demonstrate the presence or absence of antibodies, the mother's serum was incubated with serum suspended cells,[14] or was incubated with saline suspensions, washed, and bovine albumin added.[15] In a few cases rabbit anti-human-globulin serum was added to thrice-washed sensitized cells,[7] the mother's serum having been used for the sensitization. All readings were made under the low power of the microscope without removing the cells from the test tube. For all tests the same four group "O" bloods were used, they were of the following types: Rh_1, Rh_1Rh_2, Rh′, Rh_2. Positive and negative control sera were included in each series. When these tests demonstrated the existence of Rh antibodies, the sera were tested in serial dilution against Rh_1 and Rh_2 cells in saline to demonstrate the absence or presence and titer of agglutinating antibody, and in serum suspension for the blocking antibody titer.

TABLE I. DISTRIBUTION ANALYSIS OF THE 37 CASES BY YEARS

YEAR	TOTAL NO. OF CASES	PROVED BY ANTIBODIES	STRONG PRESUMPTIVE EVIDENCE	QUESTIONABLE EVIDENCE
1941	4	1	2	1
1942	5	3	1	1
1943	10	7	2	1
1944	9	5	1	3
1945	9	7	1	1
	37	23	7	7

Before tabulating the results, our first concern was to verify the accuracy of our selection of cases for inclusion under hemolytic disease of the newborn. Of the 37 cases (Table I), 23 were proved by the demonstration of Rh antibodies in the mothers' sera post partum. All these women are Rh negative. There were no definite cases which could be proved on the basis of A.B. and O. incompatibility. Of the remaining 14 cases, seven were considered as hemolytic disease of the newborn on the basis of the presence in the same case of a combination of several of the other diagnostic points; such as the appearance in early neonatal life of jaundice, pallor, edema, splenomegaly, hepatomegaly, hemorrhages, signs of cerebral damage (spasticity), circulating nucleated red blood cells in large numbers, typical placental changes,[16] Rh incompatibility between mother and child without demonstrable antibodies, postmortem pathologic confirmation, and a typical family history. (Two of these cases showed absence of antibodies, the remainder could not be tested.) The remaining seven cases, although showing some of the above diagnostic points, did not have sufficient evidence to justify inclusion as definite cases of hemolytic disease of the newborn. Thus, this study includes only the first 30 cases mentioned above, which gives us a corrected incidence of one case in 404 deliveries, which is a higher incidence than that found in another recent review of a large series of deliveries—56 cases in 28,898 deliveries, or 1 in 516.[17]

Of the 30 selected cases (Table II) 19 were livebirths and 11 were deadborn. Of the livebirths, 4 died within the first week of life, and 2 died of

pneumonia, one twenty-six days post partum, the other three and one-half months. Of the remaining 13 children, 11 were examined, the other 2 were discharged alive from the hospital, could not be traced, but are presumed alive. Of the 11 babies examined, 8 were normal and had not had a greater incidence of morbidity since birth than could be expected from any group of normal children. The remaining 3 cases, however, are markedly retarded mentally, and all have residual spasticity. It is interesting to note that there were no intermediate types, all children examined could, without difficulty, be classified as normal, or very definitely subnormal.

TABLE II. SHOWING DETAILED OUTCOME OF THE 30 CASES OF ASSUMED HEMOLYTIC DISEASE OF THE NEWBORN

YEAR	NO. OF CASES	LIVE-BIRTHS	STILL-BIRTHS	NEO-NATAL DEATHS	LATER DEATHS	DIS-CHARGED ALIVE—NO TRACE	ALIVE TODAY	NORMAL	SUB-NORMAL
1941	3	3	0	0	1	0	2	1	1
1942	4	2	2	0	0	0	2	1	1
1943	9	5	4	2	0	1	2	1	1
1944	6	6	0	2	0	0	4	4	0
1945	8	3	5	0	1	1	1	1	0
	30	19	11	4	2	2	11	8	3

TABLE III. DETAILS OF TREATMENT BY TRANSFUSION

YEAR	NUMBER OF LIVEBIRTHS	NUMBER TRANSFUSED	TRANSFUSED		NOT TRANSFUSED; DIED
			LIVED	DIED	
1941	3	3	3	0	0
1942	2	2	2	0	0
1943	5	4	2	2	1
1944	6	6	6	0	0
1945	3	2	2	0	1
	19	17	15	2	2

Seventeen of the 19 livebirths in the series were treated by repeated blood transfusions (from one to eight). Of this number, 15 were discharged alive from the hospital (Table III). The two cases not receiving transfusions died within the first week post partum. This strongly indicates the necessity of repeated blood transfusions.

It is of interest to consider the presence of maternal Rh antibodies in relation to time post partum (Table IV). Of our 23 cases which were shown to possess antibodies post partum, 13 were exclusively of the "blocking" type, three were of the "agglutinating" type, and seven showed a combination of both.

It will be noted that the "blocking" antibody persists for a longer time, as long as five years in one case, and has a tendency to be of higher titer than the agglutinating type. The average titer of the blocking antibodies of the cases of one year or less is about twice as high as the average of the cases of three years and over, indicating a gradual decline in antibody titer.

It will be seen by consulting Table V, that the incidence of the present cases of hemolytic disease of the newborn occurs with greatest frequency with the second and third pregnancies, and falling off with the fourth and fifth. Of the

TABLE IV. SHOWING THE LEVEL OF RH ANTIBODIES IN RELATION TO TIME POST PARTUM

TIME IN MONTHS	AGGLUTINATING ANTIBODY	BLOCKING ANTIBODY	TIME IN MONTHS	AGGLUTINATING ANTIBODY	BLOCKING ANTIBODY	TIME IN MONTHS	AGGLUTINATING ANTIBODY	BLOCKING ANTIBODY
56	0	1:128	25	1:8	1:64	8	1:16	1:128
49	0	1:2	20	0	1:32	8	1:256	1:128
47	0	1:16	18	0	1:4	3	0	1:64
37	1:2	1:32	18	1:16	*__	3	0	1:16
36	1:16	1:16	18	0	1:8	1	0	1:16
36	1:4	1:16	12	0	1:16	1	1:32	*__
34	1:8	1:8	10	0	1:128	(1 day)	1:8	*__
25	0	1:32	8	0	1:16	----	----	----

*These three cases were done before we adopted the serum dilution method and could not be repeated.

four incidences after the fifth pregnancy, all cases had had previous fetal mishaps dating back to their third and fourth pregnancies. The case occurring in the first pregnancy is one of the living spastic mental deficients, who was included in this series in the "presumptive" group. This baby showed generalized edema, jaundice, pallor, typical hemogram, and spasticity shortly after birth. The mother and father are both Rh positive. But no evidence of Rh subgroup iso-immunization could be demonstrated five years after birth; this is one of those cases which is typical of hemolytic disease, except for the demonstration of iso-immunization. Of the other 29 women, 27 were Rh negative, the other two being unknown and classified in the "presumptive" evidence group.

TABLE V. SHOWING THE PREGNANCY IN WHICH OUR 30 SELECTED CASES OCCURRED

PREGNANCY	1ST	2ND	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH	11TH
Number of cases	1	9	8	5	3	1	0	0	1	1	1

TABLE VI

	NUMBER OF CASES	LIVEBIRTHS	STILLBIRTHS	ALIVE TODAY
Interrupted at 36 weeks	7	4	3	1
Full-term deliveries	23	15	8	12

Seven of the 30 pregnancies were interrupted at about the thirty-sixth week, 5 by cesarean section, and 2 by other methods (Table VI). This resulted in 4 livebirths, and 3 stillbirths, which is a higher ratio of stillbirths than that occurring in the full-term pregnancies (15 livebirths, 8 stillbirths). Furthermore, there is only one living child from these 7 interrupted pregnancies. Thus, premature interruption has not yielded good results in this series.

Complications during the pregnancies of the 30 selected cases included 4 cases of varying degree of toxemia, an incidence which is not significantly above that found in pregnancies not productive of cases of hemolytic disease.[18] There was one case of placenta previa centralis, and one case of painless bleeding in the third trimester. There were no other serious complications of pregnancy, including retroplacental hemorrhage. We were particularly on the lookout for this latter complication, in view of recent claims of the presence of a significant correlation between this condition and Rh iso-immunization.[19]

The mothers in our 30 selected cases had had a total of 84 pregnancies previously, of which 31 resulted in abortions, miscarriages, stillbirths, or neonatal deaths. Eight of these 30 mothers had subsequent pregnancies, of which 6 were stillbirths and 2 livebirths. Both of these children are Rh negative, still alive and well, and, incidentally, represent the number of good children predictable.

From the foregoing information, it becomes obvious that the importance of Rh iso-immunization does not lie in the frequency of its occurrence. The importance lies in the seriousness of its manifestations in an individual so immunized from the point of view of raising a family of healthy children. There is also the danger of hemolytic reactions to blood transfusions, but the importance of this is minimized by the transfusing of Rh-negative individuals with Rh-negative blood. This is especially true relative to Rh-negative women, regardless of their age.

Proper handling of an obstetric patient who has had some mishap due to the Rh factor must be a combined effort. Modern forms of investigation and treatment executed by the obstetrician, pediatrician, serologist, and pathologist should play their useful parts.

However, the obstetrician has the initial contact with the individual patient. He is frequently asked one or several of the following questions: Should a routine Rh-factor determination be done on every obstetric patient? What is the management during pregnancy of the patient who had had previous complications relative to this incompatibility? Is a therapeutic abortion ever indicated? What is the recommendation in regard to future pregnancies? How is the baby treated following delivery?

A brief statement concerning our personal approach to these problems should be made. In recent months, some doctors and many patients are prone to explain the cause of various fetal catastrophies as being due to the Rh factor. Conditions in newborn infants, such as congenital abnormalities, asphyxia, and intracranial hemorrhage are very often wrongly attributed to this incompatibility. Hemolytic disease of the newborn is comparatively infrequent, as this series indicates. Nevertheless, when this complication does occur, the result is frequently most disastrous.

Our present attitude in the Royal Victoria Maternity Hospital is that all obstetric patients are typed with standard Rh_o agglutinating serum. When a woman is Rh-negative, an attempt is made to determine her husband's type. This is insisted upon if there is a history of any fetal mishap in previous pregnancies. If indicated, Rh-negative women are tested for antibodies at the third, sixth, and eighth months of pregnancy. This is part of a routine blood examination, which also includes red blood cell count, hemoglobin estimation, and serology to exclude syphilis. The fact that the Rh-factor is being tested is not mentioned to the patient, any more than one tells her that a Wassermann examination is being done. Too much emphasis can be put upon this test, especially when the patient is intelligent and fairly conversant with modern news reports.

If antibodies are present in the pregnant individual, the type and titer are determined; the titration is repeated each month. When the strength of the antibody titer increases to a level of 1:100, we take this as indicative of fetal

involvement. This is especially significant if the history denotes previous fetal mishaps. In seven cases, we interrupted the pregnancy at the thirty-sixth week, for the purpose of lessening damage to the fetus.

It has not been our practice to interrupt pregnancy before viability, with the indication being a high antibody titration only. But where the case history denotes repeated fetal mishaps, and with the husband not established as heterozygous, this attitude may be modified. In this last instance it is advisable that the patient should be instructed in contraceptive methods. Even ligation of the tubes should be considered.

In the face of our experience and that of others,[20] prognosis of pregnancies based on antibody studies has not in the past yielded results which justify a dogmatic stand on this particular aspect of the course of the disease. It is hoped that after some information has been accumulated from antepartum antibody studies, particularly with the newer knowledge of the blocking and agglutinating antibodies, we will be able to formulate a more definite course of action.

Analgesia and anesthesia at the time of delivery must be well chosen. Any type which diminishes the oxygen-carrying content of maternal blood should be avoided. Fetal anoxia and atelectasis may be accentuated if this type of case is poorly handled.

Early diagnosis is essential in the adequate treatment of the affected baby. The babies of all our Rh-negative mothers, whether they exhibited antepartum antibodies or not, are typed for the Rh factor immediately after delivery. In this group, daily hemoglobin estimations are done on all Rh-positive babies for the remainder of their stay in hospital.

The photoelectric method is used on blood from the heel. In a recent study by one of us (to be published later), it was found that the average hemoglobin on cord bloods was 106 per cent, while samples from the heel immediately after birth averaged 126 per cent. In this series of normal infants, no case fell below 100 per cent, hence the 90 per cent quoted below does not refer to cord blood which averages 20 per cent lower than heel puncture immediately after birth. If the hemoglobin level is below 90 per cent at birth, or if the daily drop is more rapid than normal, estimations are performed two or three times daily, and these babies are given repeated small transfusions (10 c.c. per lb.) of Rh-negative whole blood as the mainstay of their treatment. Among the supportive measures must be mentioned the interdiction of the mother's milk which has been shown[18, 24] to contain Rh antibodies of high titer in some cases. Transfusions by the exsanguination and total replacement method have not been tried because of technical difficulties and the possible medicolegal complications in case of death. In addition, it is the opinion of many that this procedure is of no greater value than repeated small transfusions. We have not used washed Rh-negative cells for transfusion as yet, but we propose to do so at the next opportunity, in view of the recent theory[8] on the mode of action of the blocking antibodies.

Summary

1. In 12,114 deliveries at the Royal Victoria Montreal Maternity Hospital, there were 37 cases of hemolytic disease of the newborn, diagnosed clinically, of which 30 cases are considered as proved, an incidence of 1 in 404.

2. Of these 30 cases there were 19 livebirths: 13 still living, 8 normal, 3 definitely subnormal, and 2 unknown.

3. Rh antibodies were demonstrable in the majority of mothers post partum.

4. Hemolytic disease of the newborn occurred most frequently in the second and third pregnancy.

5. Fetal mishaps were of high incidence in the total number of pregnancies in these mothers.

6. No other complications of pregnancy could be related to Rh iso-immunization.

7. Interruption of pregnancy at the 36th week has not yielded good results.

8. Repeated blood transfusions are recommended in treatment of the babies.

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Discussion on Papers of Dr. King and Dr. Philpott

DR. BENJAMIN P. WATSON, New York, N. Y.—In the few years which have elapsed since the significance of the Rh factor in relation to fetal and neonatal pathology was brought to our attention, two things have happened. First, the whole subject has become more and more complicated, at least to those of us who are not immunologists. I cannot add anything to the discussion of these newer concepts of the Hr factor, blocking antibodies, desensitization, etc.

Second, with the accumulation of cases, there has come a change in our evaluation of the risks to the child born of an Rh-negative mother and an Rh-positive father. The prognosis is not nearly so bad as we were at first inclined to think. It is this aspect of the subject that I should like to discuss.

In a period of eighteen months, we have had in the Sloane ward service 175 Rh-negative mothers with Rh-positive husbands. From these matings there were only 12 cases of erythroblastosis fetalis, or approximately 7 per cent. In a single year out of 1,700 viable births, there were only five cases of erythroblastosis fetalis, or approximately 0.3 per cent.

We know that the first pregnancy is quite likely to result in a healthy child, unless the mother has had a previous blood transfusion with Rh-positive blood. Out of a total of 30

cases of erythroblastosis in ward, private, and babies' hospital patients, only five occurred in first pregnancies. Three of the mothers had had previous transfusions, and in a fourth the previous history was unknown. It is, therefore, important for the future that no blood transfusions be given to a female child, girl, or woman without prior determination of her Rh status; that only Rh-negative blood be given to the Rh-negative female.

If the mother has had one erythroblastic child, the chances of future successful pregnancies are much diminished, but they are by no means hopeless, even if the husband is homozygous. In illustration I cite two cases.

CASE 1.—A Negro multipara, gravida vii, para v. Her *first* child had a secondary anemia of unknown origin, from which it recovered. Her *second* pregnancy resulted in an erythroblastotic infant that died forty hours after birth, following two transfusions of mother's blood. A *third* pregnancy ended in spontaneous abortion. Her *fourth* child had erythroblastosis, received Rh-negative blood transfusions, but developed sepsis, and died on the eleventh day. A *fifth* pregnancy ended in early abortion. Her *sixth* baby was icteric at birth and had a severe erythroblastotic anemia which responded to Rh-negative blood transfusions. A *seventh* child became jaundiced twelve hours after birth, had a moderately severe erythroblastosis, and recovered after transfusions with Rh-negative blood.

CASE 2.—A white multipara, gravida vi, para vii. Her *first* child was normal. A *second* baby became jaundiced and anemic shortly after birth, but recovered without specific treatment. Her *third* child was also jaundiced and anemic shortly after birth, and also recovered without specific therapy. Her *fourth* and *fifth* babies were jaundiced at birth and died shortly after without specific therapy. Her *sixth* pregnancy resulted in premature erythroblastotic *twins*, one of whom recovered after Rh-negative blood transfusions, and one of them died despite this therapy.

In some patients no sensitization may occur over a long series of pregnancies, as in a third case I should like to mention.

CASE 3.—This white multipara, gravida xv, was Rh negative and her husband Rh positive (genotype unknown). All her children have been normal, except for term stillbirth in the last two pregnancies; the first was due to complete separation of the placenta; the second followed rupture of the uterus.

It is cases such as these, and others could be cited, which make us less pessimistic than we were formerly, and which influence us in our advice to patients. We do not advocate routine therapeutic abortion in women who have had erythroblastic children if they are anxious to try again. If they have had previous disappointments and do not wish to risk another, the pregnancy may justifiably be terminated.

We do not advocate routine induction of labor or cesarean section before or at term. We make examinations for agglutinins from the sixth month onward, and usually find that they do not appear till after delivery. Babies born alive usually show no jaundice or fall in red cell count for twelve or more hours after birth. They can then be treated by transfusion of Rh-negative blood. We feel that no transfusion should be given till the necessity becomes evident.

If blocking antibodies are present in the mother's blood during the pregnancy, premature termination may be considered in an attempt to save the child. Finally, there is the further hope of the possibility of the development of some method of desensitization.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—One of the essayists stated that the importance of Rh iso-immunization does not lie in the frequency of its occurrence, but in the seriousness of its manifestation in an immunized individual.

The incidence on our service of Rh-negative pregnant women at the Chicago Lying-in Hospital is 15 per cent, and of erythroblastosis is 0.35 per cent. Only 2.4 per cent of Rh-negative mothers have erythroblastotic babies. Only 8 per cent of our total fetal mortality is due to this condition. The fetal mortality for erythroblastosis is 67 per cent. The question of an increased incidence of feeble-mindedness in Rh-positive children from Rh-negative mothers has been raised. Dr. Philpott reports that at present 25 per cent of their babies who had hemolytic disease of the newborn are mentally retarded. This possibility must be kept in mind.

Potter states that in 13,500 of our patients there were 2,026 Rh-negative women (15 per cent) who gave birth to 48 (2.4 per cent) babies with erythroblastosis. The incidence of erythroblastosis was 0.44 per cent in primipara, and 1.2 per cent in women who were in their fourth pregnancy.

There is no relation between anti-Rh agglutinins and abortion, toxemia, or other complications of pregnancy. Several years ago, Potter and I proved to our satisfaction that the injection of 50 to 100 c.c. of Rh-positive blood into two women with Rh antibodies resulted in hemoglobinemia. Since then several deaths due to transfusion nephritis from Rh incompatible blood have been reported. I have not hesitated to give transfusions of Rh-positive blood to Rh-negative patients if the latter were in desperate need of blood but, have simultaneously alkalinized the patient with sodium lactate given intravenously.

There is considerable confusion among the serologists about terminology. I think too many have reported prematurely.

Erythroblastosis and the Rh groupings are accepted conditions, but the theories as to etiology are very uncertain. Each new group requires additional propping. I believe careful and well-controlled studies are necessary to determine method of immunization, transfer of agglutinins back to fetus, mode of action on fetal erythrocyte, etc.

The diagnosis of anemia is of importance. The cord hemoglobin ranges from 14 to 20, with an average of 16.5 per cent, and the hematocrit from 46 to 60, with an average of 54 with heparin and 46 with oxalate. The red blood count varies from 4 to 5.5 million, with an average of 4.5. The capillary blood taken within thirty minutes of delivery ranges from 18 to 27, the average being 22 grams per cent hemoglobin, and the red cell 4.8 to 7, with an average of 6.3 millions. In other words, a capillary hemoglobin less than 18 within the first twenty-four hours is indicative of anemia. If the mother is Rh-negative and the fetus is Rh-positive, Rh-negative blood should be given and erythroblastosis should be suspected. If facilities are not available for determining the Rh group, the mother's washed cells may be used for transfusion.

The immature erythrocytes are poor carriers of oxygen and CO_2, which may account for the brain damage due to anoxia.

Exsanguination-transfusions have been used in several clinics with some success and should have further trial. We have used this method with success in two babies. Several babies seriously ill from erythroblastosis did not live long enough for us to transfuse, much less to bleed. Intravenous administration of oxygen has been reported as being of value in combating anoxia and should be tried.

DR. LOUIS CARNAC RIVETT, London, England.—I believe that some effort should be made to persuade the hematologists to agree on a uniform nomenclature for all of these subgroups of the Rh factor. I find in each department that they are quite different, and it is hard to correlate them.

Secondly, there is the possibility of the fetal red blood cells passing into the maternal blood to account for these comparatively rare cases where they develop antibodies, as compared with the certainty with which patients develop them if they have had a previous transfusion. It is quite clear that a blood transfusion of such women with Rh-positive blood will always produce an antititer. On investigation, light might be thrown on the contradiction that some Rh-negative women do not produce antibodies during pregnancy.

Dr. Philpott noticed one case where the antibodies had been present for several months. A couple of months ago I operated upon a woman to whose history I had not paid a great deal of attention. She had had two babies; the first, fourteen years ago, was stillborn after a breech delivery. Two years later she had her second pregnancy. It had been a very difficult delivery, with extensive perineal laceration, and the baby died after a few days. Twelve years later I did a repair of the perineum, and on the eighth day she had a slight hemorrhage which was easily controlled. As she was a bit pale, she was given a blood transfusion from which she never recovered. The blood was Rh negative with a very high (1 in 1028) antititer which must have persisted for twelve years.

Another thing that has impressed me in seeing these Rh-negative patients, as brought out by the cases of Dr. King is that a very high percentage of these women start their obstetric life with several miscarriages, and yet they have no antibodies at that time. I have noticed this history in a number of patients.

DR. C. L. HUDIBURG, Wilmington, Delaware.—The Rh problem as related to transfusion reactions and hemolytic jaundice or anemia of the newborn is being studied jointly by the laboratory and the Obstetrical Departments of the Delaware Hospital, Wilmington, Delaware. Since January, 1945, the laboratory has performed 1,890 Rh typings, obtaining 11 per cent negative. Routine examinations are performed with 85 per cent serum, and special studies utilize 75 per cent and 30 per cent serums. Antibody titrations use human 4-ORH$_1$ and 4-ORH$_2$ indicator cells. Early anti-Rh antibodies are demonstrated by replacing saline with 30 per cent bovine albumin, following the method of Dr. L. K. Diamond.

Two typical cases of hemolytic anemia have been salvaged because of predelivery knowledge of the antibody titer and elective early delivery and transfusion therapy. Another early delivery was lost because of aspiration atelectasis. A fourth case with a low titer was delivered at term and responded well to transfusion therapy. Titration problems presented one case of sensitization which did not increase during pregnancy and delivered as predicted, a normal child Rh$_1$ (R. K.). Two cases of evident sensitization delivered Rh-negative children. Another case of clinical icterus gravis presented a possible Hr sensitization, with the mother homozygous (pure) positive and the father heterozygous (mixed) positive. Oversensitization of both doctors and laity to this problem was observed in a case of mild anemia and jaundice in an Rh-negative mother. The child is well and has never shown any antibodies. Rh problems related to transfusions were observed in a case of myelogenous leucemia in an elderly woman who failed to cross-match properly, and evaluation revealed antibodies apparently produced during 11 pregnancies, some of which are known to be positive and negative. Transfusion with negative blood was uneventful.

The serious complication of transfusion reaction was demonstrated in a patient who had received 25 transfusions in twelve years, who had a fatal reaction from Rh$_1$ cells, but was compatible to Rh$_2$ cells.

DR. DONALD N. KARIHER, Rochester, N. Y.—In their respective discussions both Dr. Philpott and Dr. King have emphasized the importance of routine Rh tests on all pregnant women. At Rochester we have been attempting to formulate a plan for carrying out this idea for the past two to three years. We have now a scheme which is workable, and, although it has been in operation only eight months, it is proving to be very satisfactory, and I would like to present it briefly to this group.

Since Oct. 1, 1945, the Rochester Health Bureau, in conjunction with the Department of Obstetrics and Gynecology at the Medical School, have been routinely testing for the Rh factor all antenatal bloods sent in for Wassermann tests. The result of the test is reported to the physician on the Wassermann report form. If the patient is Rh positive, nothing further is done. If the patient is Rh negative, a second form is sent the physician along with the Wassermann reports.

This consists essentially of three parts. One portion of the form is for instructing the physician regarding subsequent blood samples. In testing the patient's blood for Rh antibodies, we of course carry out both the agglutinating and blocking techniques.

The husband's Rh status is reported to the physician on a second portion of the form. If the husband is Rh negative, we carry out no further studies, except in individual cases where the history is suggestive of iso-immunization to one of the other blood groups. If the husband is Rh positive, then the physician sends in samples of the patient's blood as requested on the first portion of the form.

Another portion of the form is sent in with the first sample of patient's blood submitted for Rh-antibody determinations. It is the third part of the original form sent to the physician. It makes available to us the expected date of delivery, and the pertinent obstetric history of the patient. On the reverse side of this form is a questionnaire regarding previous transfusions, their dates, and whether the patient had reactions from any of the transfusions.

The blood submitted with this form is tested for the presence or absence of Rh antibodies, and the result of this test reported to the physician. If Rh antibodies are present, the type of antibody and its titer is also reported. The physician submits subsequent blood samples at intervals throughout the patient's pregnancy on a simple form similar to that used for the husband's blood.

This plan is helpful to the physician, because it enables him to know whether he is going to deliver an infant with hemolytic disease of the newborn, and it is helpful to those of us who are interested in the study of the Rh factor, because it has and will give us an abundance of valuable material and information.

A very brief summary of some of our findings are presented in Table I.

TABLE I.

Total deliveries City of Rochester from Oct. 1, 1945, to May 1, 1946	4,717	
Prenatal Rh tests	5,567	
Rh-negative tests	690	14.1 per cent
Positive tests for Rh antibodies	20	(1 case in every 34 Rh-negative mothers) (1 case in every 278 tests)
Infants born with hemolytic disease	9	(1 case in every 524 deliveries)
Mortality from hemolytic disease	6	(1 case in every 786 deliveries)

DR. G. D. ROYSTON, St. Louis, Mo.—There are a few points in these presentations that I should like to emphasize. As the other speakers have stressed, it is vitally important to *know* the Rh blood picture in connection with every woman who is pregnant or likely to be transfused; also, whether or not she has ever had any kind of intravenous or intramuscular blood injection.

Diamond, in an excellent review of the literature published in the *New England Journal of Medicine* in April, 1945, estimated that probably 80 to 90 per cent of the transfusion reactions were due to Rh incompatibility. All blood sent to the laboratory should be tested with anti-Rh serum of the highest possible potency and of wide specificity while the blood is still fresh, preferably within twenty-four hours after being withdrawn.

I fully agree with all points made by Dr. Philpott. Although erythroblastosis is of grave import, yet, despite the mating of Rh-negative mothers with Rh-positive fathers, the incidence of severe forms of the disease is less frequent than stated in many articles. Among more than 5,000 personal deliveries, I can recall less than a dozen instances of fatal erythroblastosis. Probably more cases of the milder form, as congenital anemia, occurred and recovered without receiving any special treatment.

In the Rh-negative mother and the Rh-positive father, we check the mother's blood at frequent intervals from the thirty-second week of gestation onward, and, if antibodies are found, we deliver the patient after the thirty-sixth week and give immediate blood transfusions of 60 c.c. every one or two days (oftener in the more severe cases) until the child is out of danger.

We feel that delivery earlier than thirty-six weeks' gestation increases infant mortality from prematurity. We also feel that if transfusion is delayed until after symptoms appear, too often the infant is already damaged. In case of doubt, transfusion is safer than delay.

DR. PHILPOTT (Closing).—I gave our results for cesarean section in hemolytic disease of the newborn, but I will repeat them. We did eight cesarean sections at the thirty-sixth week. We obtained two living babies which were Rh negative. One of the six remaining babies is still alive; the other five all died.

I would like to answer two questions. First, I tried to state what we know, but I did not add that we are working on a new lead. We are studying the blood and effects of liver function. There might be a lead in this direction. Cord blood samples and those taken from the heel are different at the time of birth. We do a photo-electric estimation, and this is

done by the same technician. We have found that the hemoglobin estimation is 126 per cent in the blood taken from the heel, and 106 per cent in the blood taken from the cord; this was in a series of 100 cases. We think there is something taking place in the system to cause this terrific hemolysis, and we do know that liver function is tremendously damaged in this disease. We are trying the effects of liver protectives in the hope that they may have something to do with the prevention of hemolysis. We know that vitamin K is absolutely useless in preventing hemolysis in this disease.

With reference to Mr. Rivett's remarks about the leakage of blood, we agree with Hellman and Hertig that there are minute breaks in the intervillous spaces, and therefore little pieces of villi break off and they carry with them fetal red blood cells. When this occurs immunization may take place, and we find that the placenta, liver, and spleen and other organs are affected. We have evidence of marked placentamegaly. When this condition occurs in the placenta, blood can conceivably pass through very easily and it is no longer a good filter.

DR. KING (Closing).—It has been brought out that about only 10 per cent of patients will prove to have an Rh-positive husband and an Rh-negative wife. That reduces the trouble considerably. Although theoretically there should be 150 to 200 with hemolytic disease of the newborn, actually it is about only 1 in 500 deliveries. That has been brought out in Dr. Watson's cases. Actually, there are many who have not been immunized at all.

The method suggested by Dr. Philpott is perfectly logical regarding studies of the placental blood. Only 1/300 of 1 per cent is necessary to immunize a mother.

The question of induction of labor or cesarean section is still undecided. We must also bear in mind the question of transfusion, and if we are in doubt about the Rh type of the recipient, we can always take Rh-negative blood if we have it and it will cause no trouble. So if we have Rh-negative blood available and cannot get the Rh typing of the recipient, we can use that Rh-negative blood.

THROMBOPHLEBITIS AND PHLEBOTHROMBOSIS IN GYNECOLOGIC PATIENTS; THE PROPHYLAXIS, RECOGNITION, AND TREATMENT*

JOE V. MEIGS, M.D., AND FRANCIS M. INGERSOLL, M.D., BOSTON, MASS.
(From the Massachusetts General Hospital)

VENOUS thrombosis with its danger of fatal pulmonary embolus is an important problem in the care of gynecologic patients in New England. Prior to 1925, Davis found the incidence of fatal pulmonary emboli to be three in each 1,000 major surgical cases. In the years when exercise, posture, and other conservative measures were used to prevent embolism in the Surgical Wards of the Massachusetts General Hospital, fatal embolism occurred in approximately one out of each 800 major surgical operations. Faxon and Welch, in analyzing cases of deep thrombophlebitis, found that one out of three cases had a pulmonary embolus, and one out of 25 a fatal embolus. Miller and Rogers reported seven deaths out of 206 cases of thrombophlebitis. In patients who had had one infarct, Faxon and Welch found that the second embolus was fatal in 10 per cent of the cases. In patients aged 50 to 70 years with deep thrombophlebitis, the expected mortality is 7 per cent, and if over 70 years of age and suffering from thrombophlebitis, the expected mortality is 20 per cent.

Because of the seriousness of embolism in cases of thrombophlebitis, a means was sought to prevent fatalities from this cause in postoperative patients. Femoral vein ligation had been advocated by several German authors, including Kulenkampf and Fründ, and in this country by Homans and Taylor. The first ligation of the superficial femoral vein at the Massachusetts General Hospital was done in 1937. Since that day in the wards and in the private services of the hospital to December 31, 1945, 1,057 have been done. Early in the study, venography was a part of the method of diagnosis; this method has been discarded, for the venous picture is so very complicated and bizarre that actual and definite knowledge of the presence or absence of a thrombus is hard to determine. Further investigation of the problem was carried out in the autopsy room by Castleman, where it was definitely shown that nearly all fatal emboli come from the veins of the legs. When this fact was established and the pelvic and other veins were ruled out as the usual focus, the treatment and prevention of embolism became possible.

It is the general opinion that, if it could be certain that a clot was present in any given vein, a ligation above that vein should be done at once. The difficult problem is to decide what signs and symptoms are indications of thrombosis. At the present time, it is the consensus of opinion in our hospital that failure to ligate the veins of a patient who has had a nonfatal pulmonary embolus or a patient who has definite signs of either thrombophlebitis or phle-

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bothrombosis *at once* constitutes a serious neglect of the patient. The danger of our present feeling in regard to this phenomenon is that interruption of the femoral vein is probably carried out in patients who do not have anything wrong with their veins, and an unnecessary operation is done. Yet the avoidance of doing a simple procedure to save a patient's life, especially when it is known that the operation is of no serious import, is not to give the patient the best treatment. It is probable and possible that anticoagulents will prove to be satisfactory in the long run, but anyone who has seen a huge blood clot removed from the femoral vein cannot but feel more secure if the vein has been divided.

Material

The material for this report comes from the public and private wards of the Massachusetts General Hospital. Table I shows the number of cases operated upon each year, the number of veins interrupted, and the deaths from massive pulmonary emboli. These five deaths on the Gynecologic Service stimulated our interest in the problem of thrombophlebitis.

In Table I the types of operations which preceded the vein interruptions are listed, as is the number of patients having presumptive evidence of pulmonary emboli.

TABLE I. GYNECOLOGIC SERVICE WARD AND PRIVATE CASES

	NO. OF OPERATIONS	VEIN INTERRUPTIONS	DEATH FROM EMBOLI
1941	355	0	1 (not interrupted)
1942	738	8	0
1943	815	16	1 (not interrupted)
1944	765	23	1 (not interrupted)
1945	830	28	2 (1 interrupted)
Total	3503	75	5

TABLE II. TYPES OF OPERATIONS IN 75 CASES OF FEMORAL VEIN INTERRUPTION

	NO. OF CASES	PRESUMPTIVE EMBOLI
Total hysterectomy	41	7
Vaginal hysterectomy	7	1
LeFort operation	3	2
Plastic operation	7	0
Salpingo-oophorectomy	3	2
Vulvectomy	2	1
Curettage	4	2
Miscellaneous	8	1
	75	16 or 21% (1 fatal)

Allen, Linton, and Donaldson have shown in their studies the value of vein interruption in the surgical group. Colby has shown, and is convinced in its value in the cases of the urologic group. In the elderly male patients of the Urologic Service, and it is in this older group that fatal pulmonary embolism usually occurs, there can be no doubt of the value of vein ligation. Colby reports the incidence of fatal pulmonary emboli occurring in patients operated upon for prostatic obstruction. In 1939 to 1940, when there were no vein interruptions, there were eight fatal pulmonary emboli in 302 operations; while in 1943 to 1944, there were nine femoral vein interruptions and there were only four fatal emboli in 428 operations—a reduction in percentage from 2.63 to 0.93, ascribable to vein interruption and early ambulation.

General Plan

The general plan of the surgeons, urologists, and gynecologists of our hospital is to try to prevent pulmonary embolism whenever possible by ligating the proper veins in patients who have a suggestion of thrombophlebitis or phlebothrombosis, and to interrupt definitely the femoral veins of those patients who have had a sublethal pulmonary embolus or infarct.

Signs and Symptoms

In the gynecologic group and in all groups of ward patients, though not so universally on the private services, vein interruption is done upon any suspicion of trouble in the veins of the legs. Table III lists the number of cases who had femoral vein interruption because of pains in their legs.

TABLE III. INDICATIONS FOR FEMORAL VEIN INTERRUPTION

	1942	1943	1944	1945	TOTAL
Gynecologic Service—75 Cases					
Leg signs first symptom	7-87.5%	15-93.4%	14-60.8%	12-42.8%	48
Chest pain first symptom	1-12.5%	1-6.6%	6-26.0%	8-28.6%	16
Prophylactic interruption	0	0	3-13.2%	8-28.6%	11
Massachusetts General Hospital—1057 Cases					
	1937 TO 1942	1943	1944	1945	
Leg signs first symptom	59.0%	56.3%	41.8%	33.7%	
Chest pain first symptom	41.0%	34.5%	32.5%	23.0%	
Prophylactic interruption	0	9.2%	25.7%	43.3%	

The Residents, House Officers, nurses, and the gynecologists and their assistants examine the legs of all postoperative patients during their visits. In the course of the day if any tenderness is found, or the patient complains at all of pain in her legs, a careful examination is carried out. Examination consists of palpation of the groin, the inside of the thigh, the popliteal space, the calf, and the veins of the foot, looking for swelling and tender areas. The most important sign is tenderness in the calf discovered by pressure with the fingers and thumb of the hand. Tenderness of the calf was present in 53 per cent of our group of 75 patients whose veins were interrupted. Next, the foot is brought into dorsal flexion and, if pain is caused, it is very significant (Homans' sign). This maneuver, if done too roughly or forcefully, will cause pain in the calf of most patients, especially in women who have worn high heels, for their Achilles' tendon is short and tight. If Homans' sign is positive, thrombophlebitis or phlebothrombosis is probably present. In the 75 cases, Homans' sign was positive in 28 per cent. The legs are measured by marking an area with ink five inches above and below the patella. If there is an obvious difference in the two legs, and if the swelling is in the tender leg, the diagnosis is definite. A difference of 1 cm. is not sufficient to be of significance, but anything over that, especially if it is apparent both above and below the patella, is very suggestive. The presence of an obviously swollen leg, which has come on suddenly (plus a definitely positive Homans' sign), makes the diagnosis at once. A rise in pulse, temperature, and respiration at the same reading, and it must be on the same reading, and it must be on the same observation, in addition to other physical findings is fairly diagnostic. These changes in the clinical chart, which all of us believe to be of considerable importance as a guide to suggest the presence of a small, unrecognized pulmonary infarct, are called, in our hospital, the "Allen sign," after Dr. Arthur W. Allen, the Chief of the East Surgical Service, who has been so very much interested in this problem. A

patient with marked phlegmasia alba dolens with edema of the leg, thigh, and lower abdomen is a problem that is not pertinent to this paper. In such cases the thrombus is generally in the common femoral, possibly in the iliacs, and probably involves the lymphatics of the retroperitoneal region about the large pelvic veins. This problem should not be encountered in postoperative patients, for signs and symptoms of thrombophlebitis should have manifested themselves sufficiently to suggest vein ligation before such an end result is reached. If a patient with an old phlebitis is to be operated upon, it is the duty of the surgeon on the Gynecological Service to tie off the superficial or common femoral vein before operation or at the conclusion of operation as a prophylactic measure. This is one of the problems of prophylactic vein ligation and will be considered later.

Prophylaxis

Various methods have been tried to prevent the formation of phlebitis or thrombosis in the legs of postoperative patients. The patients, while helpless in bed, are rolled from side to side, and the legs are flexed and extended as soon as passive motion is possible. Active exercises are carried out by every patient as soon as they are conscious. Later, they are watched while doing their bicycle exercise two to three times per day. As soon as the patient reaches her bed after operation the foot of the bed is elevated upon eight inch blocks so as to aid in draining the leg veins. Pillows are not allowed under the knees. The morning after operation the blocks are taken out from the foot of the bed and are placed under the upper part to raise the head of the bed. A foot board is placed at the bottom of the bed, and the patient is urged to keep herself up in bed by pressure with her feet against the foot board. This is satisfactory during the daytime but is omitted at night, for it interferes with sleep. Bicycle exercises are kept up until the patient is out of bed. Early mobilization (first, second, or third day) has been the rule until very recently. Lately, because many gynecologic patients are fatigued, anemic, and worn out, and need rest as well as surgery, early mobilization has been changed to allowing patients out of bed when they ask to get out, and always before the tenth postoperative day. Early mobilization may have caused some postoperative complications, especially when patients sit in low, comfortable chairs that are present in most hospital rooms. It is much safer to allow them to stand up and move about without sitting or, if they must sit, to sit upon a high chair or stool so that acute flexion at the hips does not occur.

Anticoagulants are not used as a routine on the Gynecological Service. There is no doubt of their value, and a very carefully controlled group of patients are being followed on the wards by Dr. Allen. This control series will be compared with the present series later, and should give us some inkling as to the prophylactic value of anticoagulants. If an embolus follows ligations of veins, and it can and does occur, but not fatally, dicoumarol is given for ten days, making sure that the prothrombin time is definitely raised. If the prothrombin time is not changed, the value of dicoumarol is certainly open to question.

Treatment

In the past, the treatment of phlebitis or phlebothrombosis has been immobilization of the affected part and the use of hot or cold packs. The leg rested upon a pillow and the patient was not allowed out of bed until her temperature had been normal for at least a week.*

*During this treatment the patient sometimes had a pulmonary embolus or developed a typical phlegmasia alba dolens with its prolonged convalescence and its occasional permanent disability. Interruption of the superficial femoral veins markedly shortens the convalescence. In the General Surgical Group (Allen, Linton, and Donaldson) the average number of days from vein interruption to a normal chart was 5.3, and the average number of days from vein interruption to discharge from the hospital was only 8.9 days.

The surgical treatment of thrombophlebitis and phlebothrombosis consists of the interruption of the vein above the clot. Both legs must be operated upon, for if thrombosis has occurred on one side it may be present on the other and patients have died when the apparently affected vein alone has been tied, the other leg being the source of the embolus. It is always necessary to operate on both sides. Note in Table IV the shift from unilateral to bilateral femoral vein interruption on the Surgical and Gynecologic Service.

TABLE IV. FEMORAL VEIN INTERRUPTION

	NO. OF PATIENTS	VEINS	UNILATERAL	BILATERAL
		Massachusetts General Hospital, 1937-1945		
1937-1942	202	280	61.0%	39.0%
1943	165	299	19.0%	81.0%
1944	280	554	2.1%	97.9%
1945	410	816	0.98%	99.0%
	1057	1949		
		Gynecologic Service, 1942-1945		
1942	8	13	37.5%	62.5%
1943	16	31	6.3%	93.7%
1944	23	46	0	100%
1945	28	56	0	100%
	75	146		

The choice of the anesthetic depends upon the apprehensiveness and condition of the patient. If she is calm, local anesthesia is satisfactory; if apprehensive, pentothal or gas, oxygen, ether is indicated.

The femoral arterial pulsation is palpated in the groin and a 4-inch incision is made downward along the course of the artery. The subcutaneous tissue, superficial fascia and fascia lata are divided. The femoral pulsation is felt for and deep to the sartorious muscle and lying on the adductor longus muscle, the femoral artery and vein are found. The artery is anterior and slightly lateral to the vein. The long saphenous nerve lies on the outer side of the artery and should be avoided. The sheath overlying the vessels is approached from the medial side and the sheath surrounding the vein opened. Inside the sheath the dissection is carried upward and the profunda femoris perforates the muscles posteriorly about an inch and a half below Poupart's ligament. There is a bulbous swelling of the superficial femoral vein at this junction. The junction should always be well visualized and the superficial femoris isolated over a four centimeter length. When the vein is located and isolated, ligatures are placed under the vein and not tied. These are held on tension and the vein opened, tension is released to see if there is a free flow of blood. Occasionally when the vein is opened a clot may extrude from above and if this is followed by a free flow of blood it is not necessary to suck out the upper or proximal part of the vein. A large clot may slip spontaneously from the distal femoral vein out the opening. Recently a clot with all its branches at least 18 cm. long came out this way. This patient's life was probably saved. If there is no flow of blood from above after the opening of the vein, and there should be, it is essential to use suction to remove the suspected clot. The suction apparatus with a bent glass drinking tube on its end is placed up into the common femoral vein with the suction on. After the vein is sucked out and a free flow of blood occurs, the common femoral and iliac veins are considered cleared. Occasionally the profunda vein is involved by a thrombus, as well as the superficial femoral. It is important to note this because then it is necessary to tie off the common femoral rather than the superficial. To prove that the profunda is not involved, it is necessary to shut off the flow of blood from the superficial and common

femoral veins. If there is a free flow of blood from the profunda through the venous incision then it is considered open. If the profunda and the common femoral are open or cleared out, interruption of the superficial femoral may be carried out. This is done by means of silk ligatures just below the profunda, for if not a clot may form in the stump of the superficial femoral which may propagate and lead to an embolus. In a personal series of cases this phenomenon has occurred three times. Interruption is now always done at the profunda branch. It is safest to place one stitch ligature through the vein for occasionally a tie may be forced off and this may prove to be very embarrassing. If the superficial femoral and the profunda are involved, it is essential that the common femoral vein be ligated. This ligation is carried out below the area where the saphenous vein empties into the femoral, for it is not wise to tie off all the veins. A small dressing is placed over the wound, no leg bandages are applied, and the patient sent back to bed. Bed exercises are continued and the patient is allowed out of bed the same day, or at least by the next day.

Occasionally it may be necessary to go still higher than the common femoral vein and ligate the iliac veins or the vena cava. Ligation of the common iliac veins of the right side of the pelvis is much easier than the left side, due to the position of the left common iliac behind the sigmoid mesentery and behind the left common iliac artery. Ligation of the external iliac veins is very simple but it is not the operation of choice for abdominal varicosities may develop from the branches of the saphenous at its femoral junction. Prophylactic ligation of the external iliac veins at the time of total hysterectomy is very simple and although it has been done a number of times and no untoward developments have yet occurred, nevertheless it will be avoided until more information about abdominal varicosities is obtained. Vena cava ligations done either through the posterior peritoneum or retroperitoneally are not difficult and in patients with pelvic phlebitis this operation should be seriously considered. It has been done a great many times and the results are not too serious. In a few cases the legs have shown a tendency to swell and become ulcerated, but saving the life of the patient makes this complication very minor.

Prophylactic Interruption

Although most of the surgeons of our hospital agree about ligation of veins for early thrombophlebitis or phlebothrombosis we are not all in agreement about the prophylactic interruption of veins. Inasmuch as most fatal emboli occur in patients 60 years of age or older, it has been considered wise at the time of operation to interrupt the superficial femoral vein to prevent the occurrence of emboli. This procedure can be done easily after the operation has been concluded. Table V compares the ages of the general surgical cases as presented by Allen and his co-workers and our series of 75 cases, and shows the relative high incidence of thrombo embolic disease in the older age groups.

In our experience, ligation of veins adds but very little to the shock of the operation and delays it but a short time. In patients who have had phlebitis or a previous embolus following a previous operation, this maneuver would seem advisable. The ligation is often done in our hospital either 2 to 3 days after the original operation or at the time of the operation. It should be done at the time of operation for in the 2 to 3 days following the operation a thrombosis may have occurred. In one heartbreaking experience ligation of the veins was done three days after operation, the ties were placed 1½ inches below the profunda and on the fourteenth day the patient died of a fatal pelvic embolus. Because of the ligation the diagnosis of pulmonary embolus was not made, and she was considered to have a coronary thrombosis. At autopsy, a small clot was found in the stump of the left superficial femoral vein between the tie and

TABLE V. AGES BY DECADES

Massachusetts General Hospital Cases—367 *1937-1943*			
0-10	1	0.3%	
10-20	6	1.6%	17.7%
20-30	14	3.8%	
30-40	44	12 0%	
40-50	68	18.5%	
50-60	93	25.3%	
60-70	84	22.9%	82.3%
70-80	48	13.1%	
80-90	7	1.9%	
90-100	2	0.6%	
	367		
Gynecologic Cases—75 *1942-1945*			
10-20	0	0	
20-30	5	6.7%	28.0%
30-40	16	21.3%	
40-50	22	29.3%	
50-60	13	17.3%	
60-70	11	14.7%	72.0%
70-80	7	9.3%	
80-90	1	1.3%	
	75		

the profunda. There was an older clot in the common femoral vein that did not connect with the clot in the superficial femoral stump. It could be argued that either the common femoral vein was not properly explored or that the clot in the common femoral was caused by the clot in the stump of the superficial femoral vein. This calamity has made us realize that it is essential to tie the vein off close to the profunda and that prophylaxis at the time of operation is probably better than 2 to 3 days later.

Results

There has been no immediate mortality from the operation for ligation of the femoral veins and, except for an occasional lymphorrhea from the wound, no serious complications have occurred. In other hands the femoral artery has been mistaken for the femoral vein and ligated. This is mentioned only because *it has* been done. There is a little postoperative morbidity. Swelling of the legs after ligation of the superficial femoral vein may occur but it does not persist after six to twelve months. If it persists after twelve months, it is reasonable to feel that a true phlebitis had been present at the time of operation, and it is well known that swelling does occur after phlebitis. Superficial vein ligation by itself should be without any sequela. Common femoral vein ligation, however, is followed by swelling of the legs in a larger percentage of cases. If the saphenous vein and the common femoral vein are both ligated, it is quite likely that swelling of the leg will follow. In cases where the saphenous has been previously ligated, it is well before tying off the common femoral vein, to see how much venous pressure there is in the distal femoral vein before ties are placed about the common femoral. The superficial femoral can be tied safely along with the saphenous but when all three are to be ligated, due consideration should be given to the filling of the distal vein before ligation. Tension in that vein should indicate that the surgeon should not be too radical.

To our knowledge emboli have never occurred at the time of ligation or during the use of suction in the removal of clots from above. Emboli have followed interruption of the veins but few have been fatal. Emboli following

vein interruption is usually due to faulty technique and should not occur if the operation is done correctly. If emboli do occur they are not fatal and the use of dicoumarol has prevented further emboli.

After ligation of the veins of the legs, even if there are signs of a definite phlebitis, early mobilization may be carried out. Often the legs are tender after ligation for there may be a clot below the point of ligation and distention occurs due to this clot and is responsible for the tenderness. Some believe that post ligation tenderness is indicative of the fact that there was a phlebitis present before operation. It is more likely that a clot has been formed due to the ligation and distention of the vein caused tenderness.

Clots were found at the time of ligation in 19 per cent of the patients operated upon on the Gynecologic Service. It is most satisfying to find clots in the veins at the time of ligation because the operator feels he has accomplished something. It is much safer, however, to operate when thrombosis is thought to be present and to believe that the operation was done before propagation of the clot occurred.

Conclusions

1. All the surgeons of the Massachusetts General Hospital are convinced that interruption of the femoral veins is essential after a sublethal embolus or infarct.

2. Nearly all are agreed that interruption of the femoral veins is essential after the diagnosis of thrombophlebitis or phlebothrombosis has been definitely made.

3. The danger to the patient from interruption of veins properly done is minimal and it is apparent that the operation is a lifesaving one.

4. Morbidity and mortality are extremely small in the surgical attack upon thrombosis in the veins of the legs.

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(For Discussion, see p. 959.)

PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS IN GYNECOLOGY AND OBSTETRICS*

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IT IS extremely important that physicians realize the full import of the complications and sequelae occasioned by intravenous clotting. Every physician is naturally upset when one of his patients dies, but he is usually less disturbed if the death is due to pulmonary embolism than to peritonitis or some other cause. In the former case, he believes that the death was unavoidable; in the latter case he thinks that death might have been prevented. Yet, the advances made in the past decade in our knowledge of intravenous clotting make us wonder whether or not death from this complication should not be classified as preventable. Similarly, should not the same be true of the sequelae?

Intravenous clotting is of two types, phlebothrombosis and thrombophlebitis. Phlebothrombosis has been defined as a "partial or complete venous occlusion by an intravascular clot which is unassociated with inflammation, the clot being loosely attached to the vein wall."[42] Because of its loose attachment, this type of thrombus is the one most likely to break away and result in pulmonary infarction and embolism. Thrombophlebitis is "a partial or complete venous occlusion by an intravascular clot which is associated with, and dependent upon inflammation of the vein wall."[42] In thrombophlebitis the clot is strongly adherent, and, unless suppuration is present, rarely results in pulmonary infarction or embolism.

Etiologic Factors

The etiologic factors involved in intravenous clotting are cardiovascular lesions,[1-4] varicosities,[5-7] vasoconstrictors,[8] obesity,[5, 6, 9, 35] focal infection,[5, 8] cancer,[10] dehydration and demineralization,[11] anemia,[12-15] trauma,[8, 16-21] sepsis, circulatory collapse,[22] chilling,[23] posture,[24-28] immobilization,[16, 17] abdominal distention,[34] interference with full respiration,[29-33] and mechanical retardation of the venous flow and advancing age.[36]

Some authors[37, 38] consider thrombophlebitis a later stage of phlebothrombosis, but all recognize that intravascular clotting can be of two types, phlebothrombosis and/or thrombophlebitis. In thrombophlebitis the clot can undergo liquefaction as a result of infection and produce purulent septic phlebitis (suppurative phlebitis). This is especially true in cases of pelvic thrombophlebitis occurring in postpartal or postabortal sepsis, where the thrombotic process begins in the vessels of the placental site, the veins of the uterine wall or

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pampiniform plexus, or in the vagina, and extends into the uterine, ovarian, hypogastric, iliac, or renal veins, and not infrequently into the vena cava.

In phlebothrombosis or thrombophlebitis, unassociated with puerperal sepsis, the intravascular clot originates, in a considerable number of cases, in the lower part of the leg.[37, 39, 40-43] Ingraham,[44] in a study of 246 unselected autopsies, observed thrombosis of veins of the pelvis or legs in 28 instances (11.4 per cent) whereas Pretten[45] found that in 133 out of 144 fatal emboli the thrombus originated in the region drained by the vena cava. McCartney[46] noted the frequency of thrombosis of the deep veins of the leg among middle-aged and old persons forced to bed for varying periods of time, the incidence of thrombosis being 52.7 per cent, with bilateral involvement 110 times and unilateral involvement 75 times. Although less frequent in younger individuals, the same can occur in any patient of any age who is forced to bed for a long period of time or whose lower extremity or extremities are immobilized for one reason or another.

Phlebothrombosis

The fact that the signs and symptoms of bland intravascular clotting are minimal makes the diagnosis of phlebothrombosis exceedingly difficult unless its possibility is constantly kept in mind. Unlike thrombophlebitis, there is usually little or no swelling, pain, or fever, and sometimes pulmonary infarction or embolism is the initial symptom.[38, 47] Any persistent or undue elevation of the temperature, pulse, or respiration should arouse suspicion, and repeated examination for clinical signs of phlebothrombosis should be made.[38] Homans' dorsiflexion sign, a valuable diagnostic adjunct, was found in 139 of 237 cases in Allen's series. This same author found some degree of swelling and tenderness in the greater proportion of his cases. Examination of the legs should be a part of the routine of the postoperative or postpartal care of patients confined to bed. A complaint of pain in the chest or ache or pain in the lower extremities, no matter how slight, should not be casually dismissed. In some cases, marked edema of the leg is found in phlebothrombosis, especially if the common femoral vein is involved. This is more evident in cases of tumors of the pelvis in which the edema and swelling is too often ascribed to pressure by the tumor and the true etiology is undiagnosed. Any case of unilateral edema, and particularly those associated with pregnancy or pelvic tumors, should be considered to be due to phlebothrombosis of the femoral or pelvic veins until proved otherwise. Grave and fatal embolism will result if particular care is not taken to rule out this condition.

The treatment of phlebothrombosis varies in different clinics. The time honored and, in our opinion, "horse and buggy" therapy—swathing of the leg in cotton batting and elevation of the affected part—is still all too frequently employed. Certainly, it does not prevent pulmonary infarction or pulmonary embolism and, although the patient may survive the prolonged convalescence, the possibility of postphlebitic edema and ulceration leaves much to be desired when this method of therapy is used.

Present-day concepts in the management of phlebothrombosis are represented by two schools of thought. Allen,[38] Ochsner,[40, 41, 42] Homans,[39] Evans,[48] and their co-workers favor venous ligation above the thrombotic process, even if it be necessary to ligate the vena cava. Bauer,[37] Crafoord and Jorpes,[49] Evans,[48] and others advocate both the prophylactic and therapeutic use of dicoumarol or heparin. We have had no experience with the use of heparin or dicoumarol, but have used the surgical treatment for this complication.

The incidence of pulmonary embolism following gynecologic operations reported in the past three years at first glance seems small. However, when it is realized that this complication accounts for from 12.3 per cent to 25 per cent of all deaths following gynecologic operations,[50-52] its importance becomes apparent. By means of improved technique, better anesthesia, good pre-operative preparation of the patient, sulfonamides and antibiotics, plasma, and blood transfusions, the mortality rate following surgical procedures on the female pelvis has decreased materially. Deaths from hemorrhage and sepsis have declined, but pulmonary embolism remains a major problem. As stated previously, the greater number of pulmonary emboli and infarcts occur from thrombi arising in the area drained by the vena cava. The incidence of thrombophlebitis and phlebothrombosis following pelvic operation varies in reported series from 0.65 per cent to 3.9 per cent[50, 53, 56] in the former and 0.16 per cent to 1.3 per cent in the latter.[55, 56] It is interesting to note that in the series studied only two reports differentiate beween phlebothrombosis and thrombophlebitis, namely, those from Boston and New Orleans, from which most of the literature pertaining to these complications has emanated. It is extremely important to differentiate these two types of intravascular clotting, since different methods of therapy are indicated in each.

At Charity Hospital in New Orleans during the period July 1, 1939, to Jan. 1, 1946, there were 32,198 admissions to the gynecologic service, and a total of 536 deaths from all causes, exclusive of abortion. A study of the records of all deaths and autopsy records, when autopsy was obtained, showed that intravenous clotting was present in the pelvic veins in 50 cases. No mention is made of routine examination of the veins of the lower extremities. If such an examination had been made, and if autopsy had been performed on all patients who died, undoubtedly the incidence of intravascular clotting found in the channels of the inferior vena cava would have been higher. This gives a minimal, irreducible, and uncorrected incidence of 9.3 per cent in this series of 50 cases of proved intravascular clotting in 536 gynecologic deaths. In these 50 autopsies, pulmonary embolism was found to be present in 12 cases of phlebothrombosis and four cases of suppurative thrombophlebitis of the pelvic veins. The latter will be discussed later in this presentation. Of the 12 cases of pulmonary emboli, six occurred following operations on the female pelvis, particularly hysterectomy for uterine fibroids, although one followed repair of a urethral diverticulum. In this latter case, in addition, the patient had a "trophic ulcer of the left leg" which no doubt played a part in the production of the intravenous clot.

More important than the deaths recorded from pulmonary emboli following operation is the fact that five of these fatal emboli occurred in patients who were not operated on, but who were being prepared for operation for a pelvic tumor associated with edema of the lower extremity or extremities, the

latter being ignored and probably assumed to be due to pressure by the growth. In the light of our present-day knowledge of phlebothrombosis, these deaths may be considered to have been preventable. In contrast to the five cases of fatal emboli just mentioned, there were three patients, admitted to the Tulane Gynecologic Service at Charity Hospital with the same syndrome, in whom phlebograms confirmed the presence of phlebothrombosis and, at operation by the senior author, the left common iliac vein was found thrombosed to the formation of the vena cava; recovery without ill effects followed ligation of the vena cava and hysterectomy. There is no way of proving that these patients would have died had not ligation above the thrombus been practiced, but in the light of the five patients with the same syndrome who died while undergoing preoperative care, this conclusion seems justifiable. To reiterate, we believe that any patient with unilateral edema of the extremity either with or without pelvic tumors should be considered as having an intravascular clot of the common femoral and/or iliac vessels until proved otherwise, and vein interruption should be the first step in the care of the pelvic lesion.

In recent reports concerning maternal mortality, the incidence of fatal pulmonary emboli varies from 4.7 per cent to 20 per cent[57-61] of all obstetric deaths. At Charity Hospital in New Orleans there were three deaths due to pulmonary embolism in 194 deaths reviewed by the author, an incidence of 1.5 per cent. In our series, nearly all cases of pulmonary infarction or embolism followed suppurative pelvic thrombophlebitis, and this will be discussed later in this presentation.

Thrombophlebitis (Phlegmasia Alba Dolens)

As contrasted with phlebothrombosis, the diagnosis of thrombophlebitis of the veins of the extremities is not difficult. Usually fever is present; there is a great deal of pain, a variable degree of swelling, ranging from mild pitting edema to massive edema, tenderness along the course of the involved vein, and in cases of deep vein involvement, particularly the femoro-iliac veins, pallor and cyanosis in the involved extremity. The swelling is not totally due to increased venous pressure resulting from venous blockage by the thrombus, but is partly due to accumulated perivascular fluid.[40]

Ochsner and DeBakey[40] have shown that as a result of venous blockage there is a reflex vasospasm throughout the vascular tree of the involved extremity and, as a result, arteriolar pulsations are diminished producing capillary stasis and consequent anoxia of the capillary endothelium; consequently, capillary permeability is increased with exudation of fluid into the perivascular spaces, producing a vicious circle. Not infrequently, following subsidence of the acute inflammatory process, the patient continues to have considerable edema or other undesirable sequelae for the rest of her life. Here, the persistence of symptoms is probably due to perivascular fibrosis, the production of which is favored by lymph stasis. Following blocking of the sympathetic nerve supply to the involved extremity, the vasospasm can be overcome; this results in a decrease in venous pressure, diminished filtration pressure, and a tendency to prevent the increased transudation into the perivascular spaces. In addition, normal arteriolar pulsations re-establish the oxygenation of the vascular endothelium and return the permeability of this membrane to normal. Furthermore, the return of normal pulsation increases the flow of lymph and its removal of perivascular fluid.

TABLE I. PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS AND PULMONARY EMBOLISM IN GYNECOLOGY

AUTHOR	YEAR	NO. OF CASES	TYPE	THROMBO-PHLEBITIS	PHLEBO-THROMBOSIS	DEATHS	NONFATAL EMBOLI	FATAL PULMONARY EMBOLI
Gaston[53]	1945	130	Total abdominal hysterectomy	5 (3.90%)			1 (0.77%)	0
Mengert and Stoltz[50]	1945	1,925	Total abdominal hysterectomy	27 (1.40%)		38		6 (15.9%)
Tritsch and Sagarra[51]	1944		Hysterectomy			12		3 (25.0%)
Jones	1943	800	Abdominal hysterectomy	13 (1.62%)			6 (7.50%)	5
Solomons[52]	1942	790	Abdominal hysterectomy			17		2 (12.3%)
Evans and Kassel[55]	1945	381	Pelvic operations	2 (0.55%)	5 (1.30%)		5 (1.30%)	0
Counseller and McKinnon[6]	1942	2,684	Abdominal hysterectomy	99 (3.70%)				
Tyrone et al.[56]	1946	609	Hysterectomy	4 (0.65%)	1 (0.16%)		1 (0.16%)	0

TABLE II. PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS AND PULMONARY EMBOLISM IN OBSTETRICS

AUTHOR	YEAR	CASES	TYPE	THROMBO-PHLEBITIS	PHLEBO-THROMBOSIS	DEATHS	NONFATAL EMBOLI	FATAL EMBOLI
Davis et al.[57]	1946	47,945	All			81		6 (7.40%)
Gough[58]	1946	6,000	All			10		2 (20.00%)
Minnesota Maternity Mortality Study[59]	1944		All	9		112		9 (8.00%)
Rosensohn et al.[60]	1944	494	Cesarean section			17		1 (5.90%)
Hobbs[61]	1943	18,539	All			42		2 (4.76%)
Spain et al.	1944	4,243	All	6 (0.14%)				0
Ochsner Clinic	1946	1,007	All	1 (0.10%)	0		0	0
Falkiner	1944	5,420	All	4 (0.07%)			1	0

The incidence of thrombophlebitis of the extremities following gynecologic operations at Charity Hospital is about 0.12 per cent. In our private practice, the incidence is 0.16 per cent. This is lower than that of collected series[50, 53-56] from other sections, and is probably due to several factors, of which climatic conditions and prophylactic therapy play important roles. The incidence of this complication following delivery is fairly constant in all reported series. At Charity Hospital in New Orleans, the incidence is 0.06 per cent, and in our private practice, 0.1 per cent.

Infarction and embolism in thrombophlebitis of the extremities are rare but these complications, although not dangerous to life, can prolong convalescence and may produce disfigurement and disability; for these reasons alone the importance of proper and early application of therapeutic measures is evident. As in phlebothrombosis, the time-honored treatment has consisted of elevation of the leg, application of cotton batting and heat tent, and, in some instances, application of leeches along the course of the involved vein, roentgen rays and continuous caudal anesthesia, vein ligation, heparin, and dicoumarol. However, today, we believe that the treatment *par excellence* of this complication is lumbar paravertebral sympathetic block with procaine hydrochloride as advocated by Ochsner and DeBakey. The relief from pain is dramatic and the early and permanent subsidence of edema and fever together with the fact that convalescence is noticeably shortened leave little to be desired in this form of therapy. The technique is simple and may be applied anywhere; no special equipment is needed. This method of therapy has been used at Tulane University since 1938 with consistently excellent results.

Suppurative Thrombophlebitis of the Pelvic Veins (Septic Phlebitis)

Because of its frequency as a cause of prolonged convalescence and serious complications including death, suppurative thrombophlebitis of the pelvic veins is of much interest and importance to the gynecologist and obstetrician. This condition is most frequently found in cases of puerperal sepsis (either postabortal or postpartal), although it may follow the application of radium to the female genitals, operations on the female genital tract, and suppurative processes in the adnexa.[64] In large general hospitals, such as Charity Hospital in New Orleans, with large clinics, large inpatient services, and no restrictions, except financial, as to who is eligible for admission, all types of cases of postoperative postpartal or puerperal sepsis are frequently encountered.

Incidence.—In an attempt to find the approximate incidence of suppurative pelvic thrombophlebitis occurring in females at Charity Hospital in New Orleans, we reviewed all deaths occurring in females during the period from July 1, 1937, to Jan. 1, 1946. A number of the patients during the early years of this study died on medical wards where the true etiology of the condition remained unrecognized. Some were admitted with pulmonary infarction or a diagnosis of pneumonia. Since publication of an earlier preliminary survey[64, 65] of this condition and the results following operation when medical therapy failed, the internists have become aware of the important relations between pulmonary infarction and the female pelvis, and consequently in

recent years have consulted the gynecologists in case of pulmonary infarction occurring in the female in order to rule out the pelvis as a focus. Consequently, the number of cases of this condition terminating fatally on the medical wards has been reduced in the past few years.

To appreciate fully the problem of postabortal and postpartal sepsis and septic deaths in gynecologic disorders encountered in an institution like Charity Hospital in New Orleans, which serves as a "dumping ground" for all types of cases throughout Louisiana, one needs only to review the following figures. During the period July 1, 1937, to Jan. 1, 1946, of 32,198 patients exclusive of abortion admitted to the gynecologic wards of Charity Hospital, 536 died.

As stated previously, of the cases autopsied, 50, or 9.3 per cent, showed intravascular clotting in pelvic veins. In 12 instances bland clotting or phlebothrombosis was found, but, in the remaining 38 cases, suppurative pelvic thrombophlebitis was present and followed all types of gynecologic operations. A large number (11 cases) was associated with cul-de-sac or tubo-ovarian abscesses. This is not surprising, for here we have patients confined to bed for a long time with a suppurative process in intimate relation with the large pelvic veins—two of the most common etiologic factors producing thrombophlebitis. Certainly, earlier surgical drainage of pelvic abscesses, as well as particular attention to having these patients move the extremities many times a day while in bed, is indicated if the complicating factor of suppurative pelvic thrombophlebitis is to be prevented. Fatal pulmonary embolism occurred four times, due to detachment of clot, by the suppurative phlebitic process. In one case of suppurative pelvic thrombophlebitis with pulmonary infarction, following vaginal hysterectomy, vena cava ligation was performed with immediate recovery and no untoward effects. During the same period there were 44,027 deliveries at the same institution and 6,314 cases of abortion. In the former, there were 194 deaths, and in the latter, 70, a total of 264 maternal deaths in 50,341 cases, or 0.53 per cent.

Autopsy was not performed in all these cases; however, of the cases autopsied, 31 showed intravascular clotting of the pelvic veins, an uncorrected incidence of 11.7 per cent for all deaths, or 35 per cent of deaths due to puerperal sepsis. Undoubtedly, a greater percentage of autopsies (coroner's cases), especially of fatal abortion, would have materially raised this figure. In nine cases pulmonary infarction was found, and in three additional cases pulmonary embolism was observed. Again, the fact that an active suppurative process is present in the clot allows for liquefaction and infarction or embolism. Of course, the statistics just cited do not include patients having puerperal sepsis whose hospital course and history of infarction led to a diagnosis of pelvic (suppurative) thrombophlebitis and who died but on whom autopsy was not performed, nor do they include the patients operated on in whom the presence of intravascular clotting in the pelvic veins was proved or those who recovered under medical regimens.

Although the mortality rate in puerperal sepsis has been reduced by the advent of chemotherapy and antibiotics,[57, 63] it is still a leading cause of death in postabortal and postpartal sepsis.[71-79] Undoubtedly, the early and proper administration of these therapeutic agents is responsible for a considerable decrease in fatal cases, the fact remains that all cases are not cured by their administration.

Another factor to consider in statistics concerning deaths due to sepsis in obstetrics is whether one follows the patient throughout the course of pregnancy or the patient suddenly has been thrust upon him with a well-developed sepsis already present. The same can be said of the time interval between the performance of a criminal abortion and admission to a hospital. In two-thirds of the deaths occurring from postabortal sepsis at Charity Hospital, the

abortion preceded admission to the hospital by ten days or more, a few patients being moribund on admission. At Charity Hospital, as elsewhere, there has been a material reduction in the deaths due to puerperal sepsis since the advent of chemotherapy and penicillin, but fatalities still result.

The routine management of abortion on the Tulane Service at Charity Hospital has been changed but little since 1928. The conservative tenets[80] set forth by our preceptors, the late Drs. C. Jeff Miller and Hilliard E. Miller, are still closely followed, the only addition being penicillin and an earlier and more complete ligation of the venous return from the uterus in cases failing to respond to conservative therapy.

The question of the value of venous ligation in the treatment of puerperal sepsis[84-86] is an old one, there being great diversity of opinion as to when to ligate, what veins to ligate, whether or not the patients would not have survived without operation, and whether the percentage salvage following operation justifies such a procedure. Our primary interest as physicians is saving lives and we are convinced after observing a large number of cases over a period of eighteen years that the operative management of cases of suppurative pelvic thrombophlebitis failing to respond to conservative therapy will save lives that otherwise would be lost.

Miller[66, 67] and Miller[68] reported some of their cases of venous ligation; the results were sometimes brilliant, sometimes depressing. In retrospect, we believe that some of the failures were due to the fact that the operation was performed too late in the course of the disease, and the normal venous return from the uterus was not interrupted. One of us (C. G. C.) also had failures before the decision was made to ligate the vena cava and ovarian veins routinely in cases in which the conservative regimen was of no further avail and operation was indicated.

A definite diagnosis of suppurative pelvic thrombophlebitis is fairly difficult to make. Other causes of fever and/or chills must first be eliminated. A history of delivery, abortion, operation, or application of radium is usually obtained, and the patient's pulse, respiration, and temperature closely followed. If spiking fever and chills are present, less difficulty is encountered, but all patients do not show these characteristic signs or symptoms. In occasional cases, a plateau-like temperature curve is found and chills may be absent. A fairly constant finding is an elevated pulse and a patient who does not look as sick as the findings would indicate. On vaginal examination, little or no exudate is found in the parametrial areas, and occasionally one can feel the thrombosed veins, but this is not a constant finding.

Thrombosed veins should be looked for not only in the parametrial area, but along the whole vaginal wall. In one case (No. 13) we were able to palpate a large thrombosed vein extending from an infected episiotomy wound up and into the parametrial areas. In an earlier report[64] we showed that 85 per cent of these cases had infarction into the lung, and that all lung infarcts do not produce the typical pleural pain and bloody sputum, but can be silent. As many infarcts can be detected only by means of roentgenograms, chest plates are routinely made in all patients showing sepsis, and the roentgenogram of the chest is repeated if the patient fails to respond to conservative therapy. The frequency with which small pulmonary infarcts are erroneously diagnosed by roentgenograms has been previously reported by us,[64] and more recently by Krause,[69] who states "The roentgen diagnosis of pulmonary infarct is probably subject to a greater percentage of error than that of any other lesion of the lung."

Blood cultures are of value if the result is positive, especially in determining whether or not the organism is penicillin-resistant or sulfa-fast. However, if negative, it in no way rules out the presence of suppurative pelvic thrombophlebitis.

TABLE III. LIGATION OF VENA CAVA AND OVARIAN VEINS

CASE	UNIT HIST. NO.	AGE (YR.)	EDEMA	CHILL	FEVER	PREOPERATIVE PALPATION VEINS	INFARCT	PREOPERATIVE SULF.	PREOPERATIVE PENIC.	THROMBOSED VEINS AT OPERATION	ETIOLOGY	RESULT
1	T-42 30104	30	Lt.	No	Mild	No	No	No	No	Lt. common iliac	Fibroid	Excellent
2	T-46 204867	45	Lt.	No	Mild	No	No	No	No	Lt. common iliac	Fibroid	Excellent
3	T-42 24634	67	No	Yes	105	No	Yes	Yes	No	Uterines	Hysterectomy	Excellent
4	L-42 49701	30	No	Yes	106	No	Yes	Yes	No	Uterines, r. and l. ovar., r. hypogas.	Septic abortion	Excellent
5	T-42 2109	27	No	Yes	105	No	No	Yes	No	Uterines	Septic abortion	Excellent
6	T-42 37680	36	Bilat.	Yes	105	No	Yes	Yes	No	R. and l. ovar., r. common iliac, inf. and sup. v. c.	Septic abortion	Died
7	T-42 7929	22	No	Yes	105	Yes	Yes	Yes	No	Rt. ov., rt. uterine, rt. common iliac	Post partal	Excellent
8	T-42 24870	21	No	Yes	104	Yes	Yes	Yes	No	Rt. and lt. ovar., rt. and lt. ut.	Post partal	Excellent
9	T-42 33923	21	Left	Yes	103	No	Yes	Yes	No	Lt. ov., lt. common iliac	Post partal	Excellent
10	Touro-42 Mrs. J. D.	23	No	Yes	105	No	Yes	Yes	No	Bilat. ov.	Post partal	Excellent
11	T-42 73030	23	No	Yes	103	No	Yes	Yes	No	?	Post partal	Excellent
12	T-45 162310	24	Bilat.	Yes	103	No	Yes	Yes	1,240,000 U.	Rt. ov.	Septic abortion	Died
13	T-45 200093	22	No	Yes	105	Yes	Yes	Yes	620,000 U.	Lt. ov., lt. hypogas.	Post partal	Excellent
14	T-46 210042	27	No	Yes	106	Yes	Yes	Yes	2,530,000 U.	Lt. ov., uterines	Septic abortion	Good

In our series (Table III), palpable thrombosed vaginal or pelvic veins were found on vaginal examination in only 36 per cent of the cases, whereas at the time of operation, inspection and palpation of the pelvic viscera disclosed palpable and visible thrombotic veins in all cases but one. Chills were present in every case of suppurative pelvic thrombophlebitis, and, as was expected, chills were not observed in the two cases of pelvic vein phlebothrombosis, nor did the latter show any marked temperature rise, whereas, in the former group, all had temperatures ranging from 103° to 105° F.

Pulmonary infarction was not present in the two cases of phlebothrombosis, but was present in all but one of the cases of suppurative pelvic thrombophlebitis, and in four instances could be classified as massive. In addition to the cases herein reported, there have been four more patients who had ligation of the vena cava and ovarian vein for septic pelvic thrombophlebitis performed by another member[83] of the Department of Gynecology, Tulane University, during the period of January, 1943, to January, 1946, with resulting complete recovery. These four cases and Cases 11 and 12 of this series were not seen by us (on military leave), but are added to our personal series to complete the study of all cases of ligation of vena cava and ovarian veins performed by members of the Tulane Gynecologic Department, and thus better evaluate the efficiency of the procedure and present an uncorrected series.

There were no deaths in the cases in which the procedure was performed for phlebothrombosis or suppurative thrombophlebitis of the pelvic veins following gynecologic operations (Cases 1, 2, 3). The uncorrected mortality rate for all cases in which the procedure was performed for puerperal suppurative pelvic thrombophlebitis is 13.3 per cent (Table III). There were two deaths (Cases 6 and 12). In one the patient was practically moribund when operated on, and the thrombus extended from the left ovarian vein into the renal vein. At autopsy, it was found to continue into the inferior vena cava and superior vena cava ending in a core in the auricle of the heart. In addition, the patient had peritonitis at the time of operation (Case 6). The second death followed the operation by six days, and at autopsy the patient was found to have multiple embolic abscesses of the kidney, spleen, and lung. It is interesting to note that this patient was treated with penicillin and sulfonamides preoperatively, and probably the operation was performed too late (Case 12). Patients 13 and 14 were also operated on later in the disease than the cases seen prior to the author's entry into military service (1942), as we wished to give the patient every chance to recover by conservative measures and evaluate large doses of penicillin. These two patients did not respond, and ligation was performed. In Case 13, the thrombus in the left ovarian vein reached to within 4 mm. of the renal vein, but we were able to ligate proximal to it. We almost waited too long in this instance. In Case 14 the same trial of penicillin was given, and we procrastinated longer than our surgical judgment deemed it wise. The patient recovered, but now has an active endocardial lesion which we believe might have been prevented had we operated earlier, when it became evident that penicillin and sulfonamides were not producing the desired result. This result is classed as good. All other cases in which we performed vena cava and ovarian vein ligation for phlebothrombosis or suppurative thrombophlebitis of the pelvic veins had excellent and, in most instances, dramatic results. In all cases sulfonamide and penicillin therapy was discontinued at operation.

Follow-up examinations have been performed regularly to the time of writing on all patients except three, who died from two to three years following vein ligations. In none could the procedure in any way be associated with death. In Case 10 death followed operation, being performed for a pulmonary condition initiated by the patient's original infarctions prior to oper-

tion and resulting lung abscess. During that period of time she was perfectly well, had no edema of the extremities, and engaged in all types of social, athletic, and household activities. Another patient (Case 8) died of third degree burns incurred celebrating V-J day three years after ligation. Up until death she was perfectly well, in excellent health, and had no edema of the extremities or complaint of any kind. The third death (Case 1) occurred from hemorrhagic encephalitis following arsenical therapy for syphilis two years after ligation. The remaining patients show no edema of the extremities. There are no dilated abdominal, thoracic, or peripheral veins, and activities of all types are unrestricted. Three have become pregnant since and aborted, whereas one has delivered two full-term children. In no patient was there any antepartal, intrapartal, or postpartal complication of any sort. Vaginal examination on all revealed no evidence of any lesions or varicosities of the vulva or vagina. Hemorrhoids were not present.

Dr. George Burch and his co-workers[81, 82] of the Department of Medicine at Tulane University have studied these patient's circulatory status in the lower extremities at regular intervals and state: "Although the venous pressures of the lower extremities remained elevated and the volume of pulsations of the toes was reduced, there were no objective ill effects noted in the lower extremity as long as four years following operation. There was remarkably good compensation of the circulation following ligation of the inferior vena cava. The rate of water loss from the lower extremities determined on five patients eight days postoperatively was found to be normal."

In the last few years reports of cases in which vena cava ligation[87, 88] had been performed for phlebothrombosis have appeared in the American literature. All authors report good results with no postoperative sequelae and a minimal amount of edema, except Linton (quoted by Allen) who seemed disturbed by the fact that two of his patients showed postoperative edema and ulceration. We firmly believe that we have not seen these complications in the patients in whom we have ligated the vena cava because, in the earlier cases, we routinely blocked the lumbar sympathetic ganglia on either side postoperatively daily for four to five days, and in our later cases we sectioned the right and left sympathetic chains at the time of ligation.

Ochsner and DeBakey[62] have shown that any trauma to a large blood vessel of an extremity throws the whole vascular bed into vasospasm, and that this spasm is responsible for some of the edema. Therefore, we believe that in ligation of vessels the size of the iliac or vena cava, the right and left lumbar sympathetic ganglia should be blocked routinely, or at the time of operation the lumbar sympathetic chains should be sectioned in order to relieve the spasm and minimize the possibility of untoward sequelae.

Discussion

The complications arising from intravascular clotting in gynecologic and obstetric practice have been reviewed. To prevent these complications it is necessary that the patient be brought to the operating or delivery room in the best possible condition. Focal infection should have been removed, dehydration and demineralization combated, anemia eliminated by means of blood transfusions and hemopoietic stimulants, circulatory collapse and chilling prevented, abdominal distention minimized, and any interference with full respiration and any mechanical retardation of the venous return flow, such as pillows under the knee and perineal lights which involve flexion of the knee over holders, eliminated. Patients with varicosities should have their legs

tightly wrapped in elastic bandage prior to operation or delivery. Postoperatively, the patient should be made to move the extremities, wiggle the toes, or perform bicycle exercises to the greatest degree possible and many times each day. Early, selected, controlled ambulation should be encouraged and, of course, operation or delivery should be as aseptic, hemostatic, and atraumatic as possible.

Conclusions

1. By simple preoperative and postoperative measures, the incidence of intravascular clotting, either aseptic or septic, can be lowered, and in this way a number of deaths and disabling and disfiguring sequelae can be prevented.

2. The routine postoperative or postpartal examination of the patient's legs is as important as examination of the abdomen. No complaint of thoracic pain, pain in the leg, or swelling of the leg should be casually dismissed.

3. Cases of pelvic tumors with unilateral or bilateral edema of the legs should be considered as having phlebothrombosis of the deep veins of the extremity or pelvis until otherwise proved. One should be careful about ascribing the edema or swelling to pressure produced by the growing tumor. In all cases in which phlebothrombosis or thrombophlebitis is found to be the etiologic factor, adequate therapeutic measures should be instituted prior to surgical attack on the abdominal tumor.

4. In cases of suppurative pelvic thrombophlebitis failing to respond to conservative measures, and especially those in which infarction has occurred, surgical therapy should be instituted.

5. If surgical therapy is instituted, the return flow of the blood from the uterus should be ligated, i.e., ligation of the vena cava and both ovarian veins.

6. Ligation of the vena cava and ovarian veins will save a number of lives, and the complications following this procedure are slight, if any.

7. Following ligation of the vena cava, the chances of postoperative complications can be minimized if the patient has routine postoperative lumbar sympathetic blocks, or if the sympathetic lumbar chain is interrupted at the time of operation.

8. Although the death rate from puerperal sepsis throughout the country has been materially lowered since the advent of chemotherapy and antibiotics, sepsis is still a major factor in the production of maternal mortality.

9. It is hoped that with the advent of newer chemotherapeutic agents and antibiotics, by legislation directed against abortionists and by education of the public and physicians, some day we will be able to report not on how many patients died of puerperal sepsis or survived puerperal sepsis as a result of conservative or surgical therapy, but that we no longer see this dreaded complication on our service.

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Discussion on Papers of Dr. Meigs and Dr. Collins

DR. ARTHUR H. CURTIS, Chicago, Ill.—As a preliminary, I wish to call your attention to the fact that Dr. Collins' statistics indicate that the thrombophlebotic syndrome has occurred in not more than one in 1,000 cases on his service.

I am in accord with Dr. Collins and Dr. Meigs in their emphasis of the need for watchfulness in recognition of the earliest evidence of acute thrombosis. Elicitation of tenderness in the calf of the leg is important presumptive evidence of a venous lesion; it rivals a positive Homans' sign in the diagnosis of a thrombotic process.

Meigs' procedure of comparative mensuration of the legs, after marking with ink a prescribed distance above and below the patella, is an ingenious contribution.

I also agree with the essentials of the prophylaxis recommended against development of the thromboembolic syndrome. Prophylactic postoperative passive exercise of the legs is part of our routine. We also encourage all patients to move about freely in bed, but no specific exercises are ordered. I have always believed that pillows under the knees "jackknife" the patient and are harmful; unfortunately, it is a favorite with nurses and with patients.

Early ambulation has never appealed to me. It has always been our rule to permit patients to get out of bed as soon as they feel disposed to do so, but I am opposed to forced early mobilization; it may reduce the incidence of thrombosis, but I am convinced that it increases materially the amount of permanent postoperative discomfort.

It is amazing to me that bilateral femoral vein ligation has become so popular with men of eminence in our profession. It is almost beyond belief that Dr. Collins has become an enthusiast over venous ligation in puerperal sepsis and that it has appeared necessary to perform ligations in so many of the gynecologic patients operated on during the last five years at the Massachusetts General Hospital at a time when the efficacy of heparin and dicoumarol has already been demonstrated.

In the May 18 issue of the *Journal of the American Medical Association* is a report from the Mariestad Hospital, Sweden, on the intravenous heparin treatment of 209 cases of acute thrombosis among 16,495 admissions during the last five years. The number of operations was about 7,000, without a single postoperative death from thrombosis or embolism. There was a total mortality of three cases from pulmonary embolism among the nonoperated group. One of these received no heparin, one had only one injection before death, and the third patient had far advanced thrombosis on admission. In contrast with these three fatal cases, there were 47 deaths from embolism during the preceding five-year period, when heparin was not available.

Our therapy is simple, never surgical. Gynecologists are well aware that many patients are predisposed to phlebothrombosis and thrombophlebitis. Surely, all of these should have preoperative determination of prothrombin activity and coagulation time, as well as other prophylactic care. And I believe the time is near at hand when selected cases among this group of patients will be protected by preoperative prophylactic prothrombin-controlled dicoumarol therapy in small amounts, e.g., not over 100 mg. daily for one or two days.

All cases on our service with inexplicable postoperative fever, rapid pulse, chest pain, or other intangible symptoms indicative of possible phlebitis or embolism are given 100 mg. of dicoumarol immediately, this medication repeated daily under prothrombin control if the symptoms persist.

In cases with more definitely suggestive early evidence indicative of thrombophlebitis we give also one-half ampule (50 mg.) of heparin, intravenously, two or three times each twenty-four hours until repeated determinations of prothrombin activity reveal that a 100 mg. daily dose of dicoumarol has become effective. When used for prophylaxis, we give no more than 100 mg. of dicoumarol daily, and endeavor never to reduce the prothrombin time below 50 per cent.

Under a regimen as outlined, definite acute thrombosis is infrequent. In the event of its occurrence, our routine is that commonly advocated—heparin intravenously every four hours until daily administration of conservative amounts of dicoumarol becomes effective, penicillin and sulfonamides in the presence of infection, local care of the affected part, forced fluids, free elimination and early ambulation.

I have no views relative to the efficacy of venous ligations in contrast with measures previously employed. Heparin and dicoumarol therapy, one or the other, or both, is more simple, more safe and, I believe, more satisfactory.

DR. JAMES C. MASSON, Rochester, Minn.—With few exceptions, the discussions of other papers on this program have been more or less in accord with the views of the essayist and I am sorry to raise a discordant note at this time. My views are radically different from those just presented.

To begin with, I think that all venous clotting starts as a so-called phlebothrombus and it is not until the vessel is occluded and clinical change takes place in the thrombus and stagnated blood that elevation of temperature, pain, tenderness and swelling make the diagnosis of thrombophlebitis possible. In my experience, most of the fatal pulmonary emboli occur with little or no previous warning. Most fatal pulmonary emboli, on the other hand, may result from small floating thrombi or from small proximal extensions from a fixed thrombus and they may occur from above a ligature. In my experience it has been difficult to decide when and what veins should be ligated to protect against pulmonary embolism, and I think the promiscuous ligation of major veins as a prophylactic measure is not warranted, especially in view of the possible sequelae that may be a definite handicap to the patient in future years. Furthermore, ligation of any veins above the common femoral must be considered a major procedure on an already sick patient.

Parasympathetic lumbar blocking with a local anesthetic is an efficient and valuable method of causing vasal dilatation with relief of pain and reduction of lymphedema. In the case of a very sick, frightened patient under tension this procedure is looked on at least as a minor operation; furthermore, I think that much the same results can be obtained by properly applied heat and proper elevation in a sling with suspension from above the bed. In patients in good condition, the addition of whisky by mouth has some vasodilating effect, and tends to relieve tension and improve morale rather than frightening and depressing the patient.

I do not feel that ligation of a major vein should be considered lightly. I have only once ligated the left common iliac vein. It is now one and a half years since the operation and the patient is definitely handicapped and uncomfortable with a large swollen leg. I have not had experience with definite infection in veins such as occurs in cases of puerperal infection. In such cases ligation above the infected thrombus as advised by Dr. Collins might well be a lifesaving measure. On the other hand, a thrombus or embolus starting in the

deep veins in the leg is *never*—and I repeat, in my experience, *never*—infected and the name "thrombophlebitis" is misleading. Repeated cultures from clots and walls of veins are always negative. The elevation of temperature, pain, tenderness, lymphedema, etc., are the result of clinical changes in the clot and stagnated blood with an influx of leucocytes and of vasospasm with resulting lymphedema. This condition must be distinguished from septic thrombophlebitis. It has not been at all uncommon in my experience to find thrombosed veins in the bases of the broad ligaments in the course of a pelvic operation, and I have so far never had cause to regret not doing a prophylactic ligation of a major vein proximal to the clot.

Anticoagulants (heparin and dicoumarin) are being used in the Mayo Clinic in cases of nonfatal pulmonary embolism and on at least one service dicoumarin is used prophylactically in all cases in which there is a high tendency toward thrombus.

In the last four years (1942, 1943, 1944, 1945), with ten surgeons operating, hysterectomy has been performed 4,810 times with 26 occurrences of diagnosed pulmonary embolism but only six deaths or 0.1 per cent.

My own service with a fair share of the more difficult cases can be looked on somewhat as a control, as I do not use anticoagulants. In the same four years, I did total abdominal hysterectomy in 709 cases with only two deaths. The cause of one death was diagnosed as pulmonary embolism but there was no necropsy and the cause may have been cardiac. The other death was from peritonitis. In only one other case was pulmonary embolism diagnosed and in that case pleurisy was present. The patient made a good recovery. In the same years, 1942 through 1945, I did vaginal hysterectomy in 413 cases with two cases of pulmonary embolism. Only one patient who had pulmonary embolism died, a mortality rate of 0.2 per cent from pulmonary embolism. During the last two and a half years, that is up to the present time, I have done abdominal hysterectomy in about 400 cases. There have been no deaths from any cause and no major veins have been ligated.

In closing, I do not want to pass judgment on a method with which I have had practically no personal experience. My own reaction is that I do not see many cases in which prophylactic ligation of veins is required. Furthermore, I know that in some clinics, like the Lahey Clinic in Boston, where formerly such procedures were used in a considerable number of cases, they are now almost entirely disused.

It is hard for me to believe that in my series quoted previously, with an over-all mortality rate of 0.3 per cent and a mortality rate from pulmonary embolism of 0.1 per cent, prophylactic ligation of veins was indicated.

DR. E. L. KING, New Orleans, La.—I worked with the late Dr. C. Jeff Miller for many years and, as you probably all know, he did ligation of the veins in some of these cases. We had considerable experience with suppurative thrombophlebitis, especially at the Charity Hospital where we have many cases of septic abortion. I think we should emphasize that we are fearing not only pulmonary embolism, but spread of the infection through the system and multiple infections elsewhere, in addition to the embolism.

I have had one case of vein ligation in consultation, a patient that had been badly handled. In that case we did ligate the vena cava and did a hysterectomy. The patient recovered and had no trouble whatever so far as the swelling or circulatory condition of the leg was concerned. We do believe it is indicated in these particular cases, shown clinically more than anything else by the high temperature and chills. It is a definite picture, a clinical entity and the condition seems to be best handled by ligation.

DR. CURTIS (in reply to Dr. E. L. King's discussion).—It is my very definite impression that Dr. Miller ligated the veins in puerperal sepsis, in a few instances experimentally, and made up his mind that it was not a valuable or indicated procedure.

DR. KING (continuing).—Dr. Miller changed his mind very frequently, I may say. He would ligate the veins and get very good results; then in some others he would not get such good results. Perhaps he did not go high enough in those latter cases. In the later years he did ligate more often, always the hypogastrics and the ovarians.

DR. LEWIS C. SCHEFFEY.—Philadelphia, Pa.—During the past five years, we have become very alert in trying to differentiate between phlebothrombosis and thrombophlebitis, and the implications concerned with them, on the Obstetrical and Gynecological Service at Jefferson Medical College Hospital.

One of the things that has been stressed is the education of our house men in recognizing these conditions. There has been close cooperation between our department and general surgery. We have instituted a broad prophylactic program with which our staff members, residents and interns have become familiar.

The necessity of active motion postoperatively, deep breathing, avoidance of cramped positions and pillows under the knees, avoidance of distention, and early rising as soon as agreeable after operation, is stressed constantly.

In addition, the house staff has been instructed to check the condition of the extremities daily, and carefully to evaluate any and all complaints of pain or distress that might possibly be significant. We endeavor to distinguish between thrombophlebitis and phlebothrombosis on the basis of respective symptoms and physical signs, for our management of these conditions differs distinctly.

Thrombophlebitis.—Here we have relied entirely upon the sympathetic block and in no case per se has Dr. Willauer, the surgical consultant urged the ligation of the femoral vein. Pain in the groin, medial aspect of the thigh or buttock, particularly when preceded by an unexplained fever or rapid pulse, suggest thrombophlebitis. Examination shows perhaps some abdominal distention, with tenderness over the femoral vein or groin. The foot of the affected limb or limbs may be cold and/or moist, though color may be normal. There may be edema of varying degree.

For such a symptom complex we elevate the foot of the bed about eight inches, keeping the patient flat, but moving about actively and encouraging pulmonary ventilation. Light dressings are changed, water balance is checked and corrected if indicated.

Lumbar sympathetic nerve block (with eucupin-procaine solution) is carried out promptly if symptoms and signs continue to progress, but if coldness and moisture of the affected part or parts predominates, continuous spinal anesthesia at the 5th or 6th thoracic segment is given for two to three hours, instead of sympathetic block.

No ligations of any of the femoral or pelvic veins have been done in these cases of thrombophlebitis, nor have there been any *discovered* embolic phenomena, and no deaths from embolism with this regime of treatment.

Phlebothrombosis.—Here the symptoms are slighter and much more vague, but indicative of a graver and more serious situation. Usually afebrile, an ache in the foot or calf of leg is significant; also the feet may feel tender to the patient. On examination there may be slight swelling about the ankle or lower leg, with a degree of cyanosis perhaps. On the affected side the foot cannot be flexed with the same ease as on the opposite side. Homan's sign is present, tensing of the Achilles tendon causes pain in the calf or back of the knee. No signs are usually present in the thigh. Pulsation of the dorsalis pedis and the posterior tibial arteries may differ comparatively in the affected leg, being almost imperceptible or even absent.

With the above findings, we immediately carry out ligation and division of the superficial femoral vein below the profunda femoris, with removal of all clots so that a retrograde flow may be obtained. If this does not happen, then ligation at higher levels in the pelvis is done (with local or spinal anesthesia). Patient becomes ambulatory at once or as soon thereafter as possible. We have not as yet performed prophylactic femoral ligation in our patients. There have been no embolic phenomena and no embolic deaths since carrying out this form of management.

DR. COLLINS (Closing).—In answer to Dr. Curtis, the figures we gave of the number of involved veins with infection—9.3 per cent—were uncorrected. The figures were not compiled from the number of autopsies, but from the whole series of deaths, the figure being uncorrected. The correct figure in the patients dying from septicemia is 35 per cent showing involvement of the veins; which figure closely approximates those from other parts of the country.

As to the drugs mentioned, I have no experience with dicoumarol or heparin. Some investigators and clinicians do not think heparin and dicoumarol should be given in postabortal cases, especially where there is infarction of the lung associated with a septic process in the vein, as a number of those patients will die from hemorrhage from the lung as a result. Where a major vessel is ligated and not had immediate block there may not be any persistent edema. While that is true, I think one can minimize or reduce the number of cases of postoperative edema if section of the sympathetic chain is performed to increase the peripheral circulation, relieve the vasospasm and decrease the capillary anoxia.

DR. MEIGS (Closing).—I have recently been in New Orleans and have had the privilege of seeing two of Dr. Collins' patients and they have an absolutely perfect result, with no evidence of any swelling of the legs. I think that is due to the fact that he does not injure the circulation by tying off the vena cava because these patients have already a block of the vena cava. All he does is to prevent embolism and septic infarcts.

Dr. Collins is using a therapeutic ligation. Nature has taken care of the legs and Dr. Collins is preventing the patient from having septic infarcts, which I think is very commendable.

We must select cases for superficial femoral vein ligation. If a patient develops a mild thrombophlebitis, some will have an embolism. If you can ligate the superficial femoral veins, which is a simple procedure, without injury to the patient, it should be done. We have no swollen legs. In suspicious patients there is a rise of pulse, temperature and respiration, the "Allen sign." Dr. Allen feels that if the above occurs then the patient has had a small infarct, and the patient's veins should be ligated. If a patient has tenderness in the calf, something should be done about it. I am sure we all believe that if a patient has an infarct—and I think it would be the same with you if any of you developed an infarct after an operation—the femoral vein should be ligated.

ON THE ORIGIN OF CERTAIN PERISALPINGEAL CYSTS*†

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(From the Departments of Gynecology and Pathology, Michael Reese Hospital)

SMALL cysts of varying size are found in the wall of the uterine tubes. The derivation of these cysts has received much attention, and there are many hypotheses to explain their origin. They are said to arise from the junctional system, the epoophoron, paroophoron, Kobelt's tubules, and the pronephros (hydatid of Morgagni) (Gilbert and Shorey[1]). An excellent review of this subject is given in the Stoeckels *Handbuch der Gynaekologie*.[2] The purpose of this communication is to draw attention to certain cell balls containing cystic structures, to discuss the possible origin of these structures, and to offer them as an additional starting point of pelvic adenocarcinoma.

Isolated accumulations of cellular elements forming small clumps or balls are frequently found in the wall of the uterine tubes. They are commonly situated in the outer portion of the tubes, just beneath their peritoneum. From the shape of the cells it seems clear that they are epithelial. They resemble those lining the lower urinary tract and should be classified as transitional epithelial cells.

Ten apparently normal uterine tubes were cut into several blocks and many random sections taken. Six tubes contained these cell balls.

The individual cells are round or oval-shaped, approaching spindle forms. They exhibit an eosinophilic or clear cytoplasm and clear-cut vesicular nuclei. The cells are densely packed, but their cellular membranes are always recognizable. They are surrounded by what appears to be a basal membrane. Such cell balls have been observed and described by various investigators, and their origin considered to be the same as that of the cystic structures previously mentioned.

On examination of a series of these cell balls, it was noted that a pinkish, homogeneous material often appears in the centers of these cell nests and that nuclei of adjacent cells become pale-staining or absent. It seems that the cells situated within the center tend to degenerate and liquify, forming small cystic structures. The cells forming the innermost lining of the cyst assume first, low cuboidal, and later, high cuboidal shapes, while the cells situated peripherally remain transitional in character. As such cysts enlarge, fewer transitional cells are found. These then become cystic structures lined by cuboidal cells with a few transitional cells present at only one pole of the cyst. In later stages when the pressure within the cyst has increased, the inner lining cells are found to be compressed and flattened, and resemble endothelial cells. Finally, all lining cells disappear and the cyst is lined by a thin membrane only.

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

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Sometimes the presence of both transitional and cuboidal cells can be observed in a single uterine tube.

These cell balls and cystic structures call to mind the so-called cell nests of Limbeck[3] and Brunn.[4] Such cell balls have often been observed beneath the mucosa of the urinary bladder, the ureter, and more rarely, the pelvis of the kidneys. They constitute circumscribed accumulations of transitional cells. The centers of these cell balls occasionally show cystic degeneration. When these cystic structures project over the mucosa, they give rise to the so-called cystic cystitis.

Saphir and Kurland,[5] who had studied several such instances, described the gradual changes from transitional to cuboidal cells forming the inner lining of such cystic areas. Furthermore, they have traced the origin of rare adenocarcinomas arising in the urinary bladder to the cuboidal cells lining such cystic areas. The change from transitional cells to cuboidal cells was explained as a reversion to an embryologically younger form of epithelium, and taken as an example of so-called de-differentiation. It has often been stated that as a result of inflammation, regeneration, or tumor growth, new cells undergo a de-differentiation or reversionary process in the direction of the primary embryonal or blastomere cell. With further growth there is a re-differentiation to form a type of cell not identical with the original type. This new differentiation produces cells of a lower order of specialization than the original, but may occasionally progress higher. This is progressive or prosoplastic metaplasia (Karsner).[6] Pincsohn[7] pointed out that the columnar epithelium in the bladder developed by means of "indirect" metaplasia. He considered that the dominant cell type of a tissue may become inferior to the recessive cell type which in turn becomes dominant.

The bladder develops from the cloaca which is lined by cylindrical epithelium. This epithelium is dominant in the rectum, inferior and recessive in the bladder, where the transitional cell epithelium is dominant. Any irritation may be the cause of epithelial proliferation or regeneration. The epithelium now may become atypical and the transitional cell revert to an inferior recessive type, while the inert inferior recessive type, the cylindrical cell, becomes dominant. Thus, cylindrical cells are seen. Within the cell nests of Limbeck and Brunn it is apparently the cystic degeneration which causes the de-differentiation.

It is, of course, hazardous to conclude similarity of origin from the fact that structures closely resemble each other morphologically, i.e., the cell balls in the urinary bladder and those within the wall of the uterine tubes. However, the cells of both types of cell masses seem similar histologically. Furthermore, it is significant that the innermost cells lining degenerated cystic areas become cuboidal in both instances. It seems possible that some of the lining cells of the cloaca are misplaced along the Müllerian duct, and there change to transitional cells just as those in the normal urinary tract mucosa. Whenever degeneration with cyst formation occurs in cells which are separated from the normal urinary tract mucosa, as in the cell nests of Brunn and Limbeck and those described in the wall of the tubes, the cells adjacent to the cystic, degenerated areas revert to the embryologically younger form of epithelium. It may be mentioned here that as early as 1904, Robert Meyer[8] studied such epithelial

cysts. His illustrations show that he was dealing with a type of cyst lined by transitional cell epithelium.

He believed that (1) they represent Wolffian duct rests, (2) they may be derived from the epithelium lining the coelom cavity rather than from suprarenal rests and, (3) they are produced by inflammation. A similar epithelium later forms the anterior wall of the sinus urogenitalis and the urinary bladder.

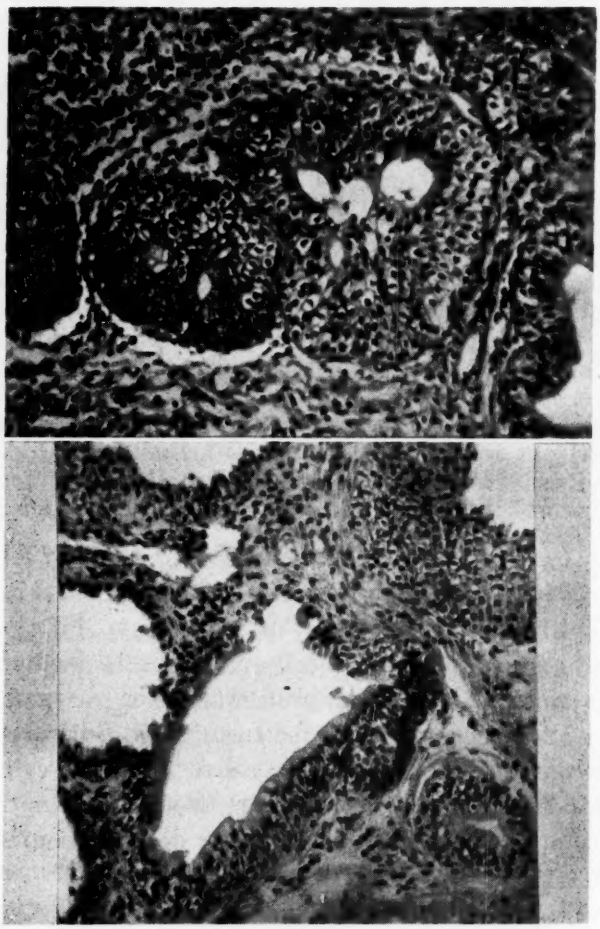

Fig. 1.—Urinary bladder. Note the small islets of transitional cells with central cyst formation. Also note the cuboidal appearance of the inner lining of the early cyst. (Iron-hematoxylin-eosin preparation). (×130).

Fig. 2.—Urinary bladder. Cell balls with cyst formation. Note the cuboidal lining cells. (Iron-hematoxylin-eosin preparation). (×130).

If it is true that these cell balls in the wall of the tube are epithelial in nature and are transitional epithelium similar to that lining the urinary bladder, one would expect that occasionally carcinomas might arise from these structures. Carcinomas of the urinary bladder are most commonly papillary transitional cell carcinomas. Only rarely are adenocarcinomas with transitional epithelial features encountered there. These are said, as stated before, to arise from the transitional epithelial cells of Limbeck and Brunn.

Two instances of carcinoma which seem to have arisen from the transitional epithelial balls of the uterine tube were recently found.

CASE 1.—An uncomplicated transitional cell carcinoma was found in a 47-year-old woman admitted to the private Service of Dr. William H. Rubovits because of uterine bleeding. There was no tumor palpable at that time. A vaginal hysterectomy was performed. During the operation, the tubes and

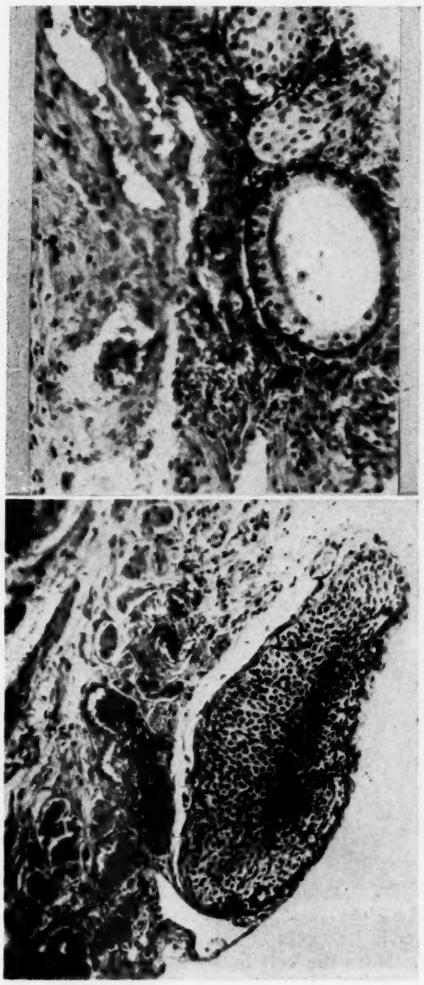

Fig. 3.—Urinary bladder. Cell nests with small cyst. (Hematoxylin-eosin preparation). (×130).

Fig. 4.—Large cell ball in wall of tube. Note the transitional cells which make up the cell ball. (Iron-hematoxylin-eosin preparation). (×90).

ovaries were inspected and palpated, and were found to be normal. Histologic examination of the uterus showed a hyperplastic endometrium with early fibrotic changes. There were several polyps present and also an old cervical erosion. This patient was re-admitted eleven months later complaining of pain in the right lower quadrant. Bimanual examination revealed a palpable mass in the right pelvis. Laparotomy was performed, and both ovaries and tubes were removed.

The right tube was a dark, reddish blue, tubular structure, measuring 20 cm. in length. It was markedly dilated and presented several kinks. Its external surface was glistening and contained minute blebs. The smooth distal fimbriated end of the tube measured 8.5 cm. in diameter. A pale, gray-pink tumor of semi-firm consistency protruded from the tubal surface. This tumor measured 6 by 8 cm. in its greatest dimensions and was covered by tubal serosa.

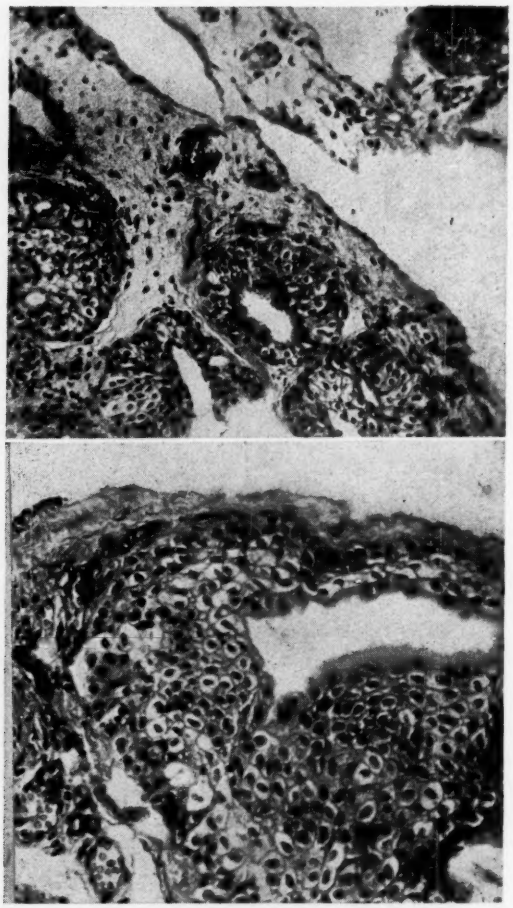

Fig. 5.—Small cell balls in wall of tube. Note cystic degeneration in center, and the cuboidal appearance of the cells lining the cyst. (Iron-hematoxylin-eosin preparation.) (×130.)

Fig. 6.—Wall of tube. Note the cell ball with cystic degeneration, and low cuboidal type of cells lining the cyst. (Iron-hematoxylin-eosin preparation.) (×240.)

On section, it was seen that it arose in the wall of the tube, and secondarily invaded the mucosa and extended into the lumen of the tube. The tumor was of a greyish pink color, finely granular, with foci of necrosis and hemorrhage. The tube contained much serosanguineous material. The ovaries and the left tube showed no significant changes.

On histologic examination, it was found that the tumor consisted of epithelial cells which, though varying in size, were principally elongated or slightly oval, with oval, vesicular nuclei (Figs. 11 and 12). Atypical mitotic figures were abundant. There were many small blood vessels present, and the tumor cells seemed to be closely attached to the vessel peripheries. In some fields the formation of cores of an insignificant amount of connective tissue with one or two

small vessels was noted. Some of the cores with the adjacent tumor cells seemed to form smaller or larger papillary structures. From the appearance of the tumor cells it was concluded that they were transitional epithelial cells, similar to those seen in tumors arising from the mucosa of the urinary bladder. It was obvious that this tumor did not constitute a metastatic growth. The origin seemed to be the transitional epithelial cell balls in the wall of the tube.

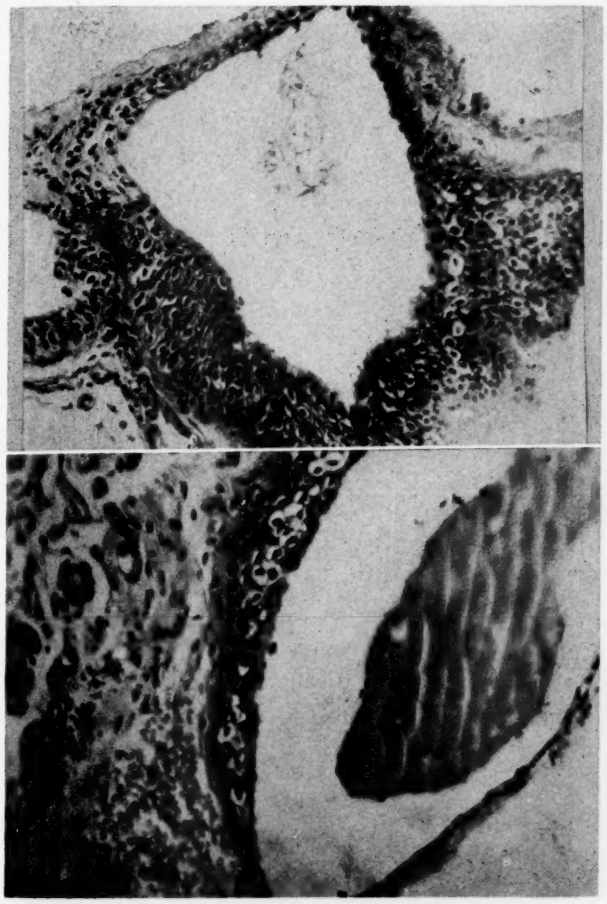

Fig. 7.—Wall of tube with transitional cell balls and cyst formation. Some of the lining cells are flattened, resembling endothelial cells; others still are of low cuboidal type. (Iron-hematoxylin-eosin preparation). (×130).

Fig. 8.—Wall of tube with cystic cell ball. The lining cells in the right lower field are compressed, resembling endothelial cells. Cuboidal cells are still recognized forming the innermost lining of the cyst at the left. (Iron-hematoxylin-eosin preparation). (×130).

Often, adenocarcinomas are found in the pelvis with complete destruction of one ovary and tumor formation within the pelvic peritoneum, broad ligament, and wall of the tubes. In the absence of any other primary site of the carcinoma, it is usually assumed that the primary carcinoma is located within the ovary. Sometimes, papilliferous and adenocarcinomas are found, in addition to diffusely infiltrating carcinoma cells which seem of the transitional type. It has been pointed out that in these latter instances, when the transitional cells invade the core and the ovarian structures, they often assume spindle shapes. Such tumors

may be confused with the spindle-cell sarcomas and lead to the erroneous diagnosis of carcinosarcoma. At any rate, adenocarcinomatous structures and transitional cell carcinomatous structures are occasionally encountered side by side in such tumors. It is of interest to note that similar tumors consisting of adenocarcinomatous structures and transitional epithelial cells also occur in the urinary bladder. These tumors, as stated above, are thought to arise from the

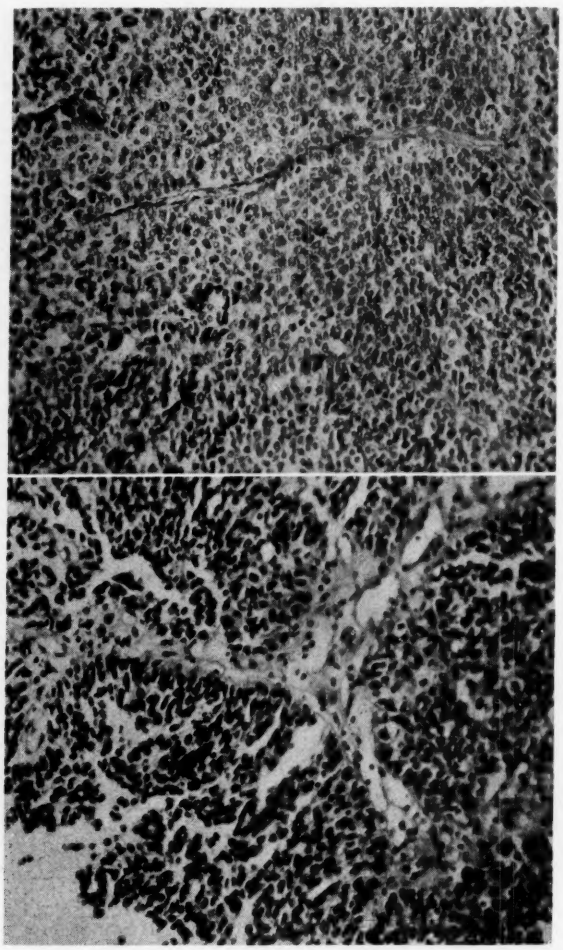

Fig. 9.—Section of primary tumor of the Fallopian tube. Note the transitional type of tumor cells and their relation to the thin walled blood vessel. (Hematoxylin-eosin preparation). (×110).

Fig. 10.—Section of primary tumor of the Fallopian tube. Note the transitional type of tumor cells simulating those seen in the urinary bladder. (Iron-hematoxylin-eosin preparation). (×130).

cell nests of Limbeck and Brunn. From this study, and also from studies of instances of adenocarcinomas of the urinary bladder, the origin of adenocarcinomas with transitional carcinomatous structures from cystic degenerated cell nests of the wall of the tubes must be considered.

CASE 2.—The second patient had a primary tumor involving the entire left pelvic region. At first it was thought to have originated within the left ovary. It was found in a 53-year-old patient, who had had a hysterectomy thirteen

years before. She developed a mass in the left lower quadrant with marked ascites, had continuous fever, severe abdominal pain, became progressively and rapidly weaker, and died.

At autopsy the region of the left ovary was completely replaced by a tumor mass which was partly firm, gray, and presented a finely granular, partly cystic, cut surface. The left tube and broad ligament could not be clearly identified. The right ovary was enlarged and the seat of a metastatic tumor. Metastases were found in the peritoneum, liver, and sigmoid colon.

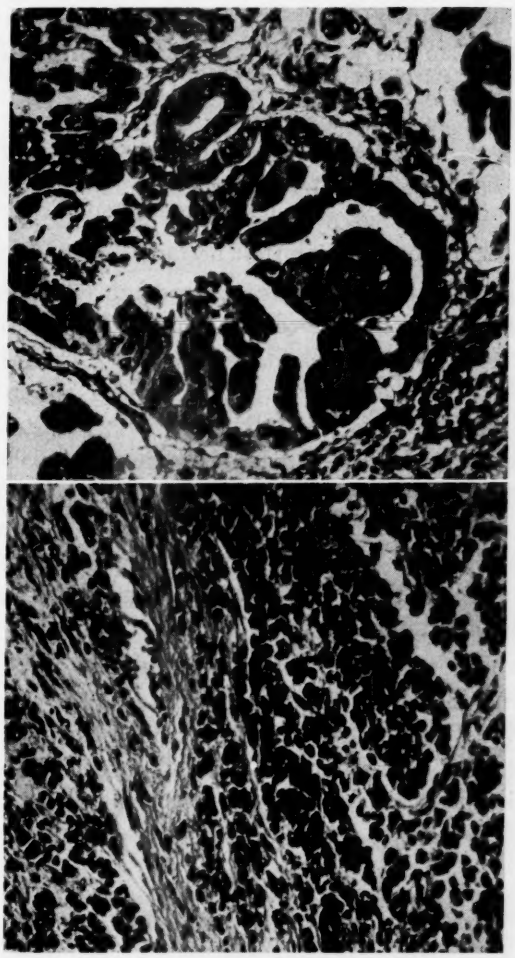

Fig. 11.—Adenocarcinomatous structures in tumor found in the region of the ovary. (Iron-hematoxylin-eosin preparation.) (×130.)

Fig. 12.—Section taken from the same tumor as shown in Fig. 11. Note the transitional type of tumor cells. (Iron-hematoxylin-eosin preparation.) (×130.)

Histologically, the tumor consisted of large masses of epithelial cells (Figs. 9 and 10). Many of them were spindle or oval shaped with vesicular nuclei that varied much in size, shape, and staining quality. There were also distinct glandular structures lined by cuboidal cells which disclosed evidence of malignancy. Both of these malignant structures were found in the primary tumor and in the metastatic growths. A diagnosis of primary adenocarcinoma of the ovary with marked anaplasia cannot be ruled out completely, but it might be possible that this tumor arose from transitional cell balls of the left tube.

Adenocarcinomas of the urinary bladder are thought to arise from the cell nests of Limbeck and Brunn. In addition, they may arise from the cells adjacent to the cystic degenerated areas of these cell balls in instances of cystitis cystica if transitional carcinomatous structures are present, in addition to malignant glandular structures.

In the same way, the presence of degenerated cell balls and malignant glandular structures within the uterine tubal wall would tend to support the theory that this type of mixed malignancy may arise from nests of epithelial cells which originate from the lower urinary tract epithelium.

Summary

Attention is drawn to cell balls which are often encountered in the wall of the uterine tubes. These consist of transitional cells and very closely resemble morphologically those described by Limbeck and Brunn in the urinary tract. The cells in the center of these balls often become liquified and form cysts.

The cells forming the inner walls of such cystic, degenerated areas assume cuboidal shape. The origin of adenocarcinomas in the urinary bladder is traced back to these cystic, degenerated cell balls. Changes similar to those occurring within the cell balls in the urinary tract have been observed in the cell balls located in the wall of the tubes, including the change into cuboidal cells. Because of the resemblance of these cell balls to those described by Limbeck and Brunn, because of the close resemblance of the individual cells of these nests to the transitional cells lining the urinary tract, and because of the similarity in morphologic alteration of the cells lining the cystic degenerated areas, it is suggested that these cell balls and cysts seen so often in the wall of the tubes may arise from misplaced lower urinary tract epithelium.

A primary papillary transitional cell carcinoma of the uterine tube is recorded. This probably took its origin from such epithelial cell balls. A second carcinoma involving both the tube and the ovary is described. This tumor consisted of both transitional epithelial features and glandular structures. It is possible that this tumor may also have arisen from such cell balls of the tubal wall.

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Discussion

DR. JOHN L. BREWER, Chicago, Ill.—These tumors that arise in the Fallopian tubes are rare, and, as such, one person does not have access to a great amount of material. The conclusions that can be gained from a study of such tumors is further complicated

by the fact that many are of such size that the determination of their source of origin is impossible. Apparently, there does occur in the tube certain tumors which have transitional character epithelium, and also some having an associated adenocarcinoma.

The author has suggested a possible origin of transitional cell carcinoma and adenocarcinoma of the Fallopian tube. This thesis logically followed the work done by Saphir and Kurland, in which they traced the origin of adenocarcinoma associated with transitional cell carcinomas from cell nests in the urinary bladder. The author has demonstrated a similarity between these cell nests of the bladder and cell nests found in the Fallopian tube wall. Several questions are immediately posed concerning these cell masses. The first is that concerning their origin. The author believes that they arise from cloacal epithelium. There are different opinions regarding the origin of the cell nests along the tissues of the urinary tract. The most prevalent theory is that they arise as a result of localized inflammatory reactions. There is evidence that this latter statement is true for the cell nests in the bladder, and it has also been suggested for the cell nests in the tube. From the tissues that I have observed, however, a striking feature is the absence of any evidence of inflammatory reaction in association with the tubal cell nests. The only evidence that I know of that the cell nests of the tube originate from cloacal epithelium is that which the author presents, and which is based upon the histologic similarity of the two groups of cell nests. More conclusive evidence is required before the origin can be definitely stated.

Second, the cuboidal and columnar epithelium found in association with the cell nests in the tube is similar in appearance and relationship to that seen in the cell nests in the urinary bladder. This has led the author to believe more strongly that the two groups of cell nests are identical. The relationship of the cell types also offers a possible explanation for the occurrence of adenocarcinoma and transitional cell carcinoma in the same tumor in both the tube and urinary bladder. The cell stages in transition to the malignant tumor formation in the bladder has been traced, but in the specimens presented in this paper such transitional stages are not seen. Again, however, the similarity of the malignant tumor tissue in the two locations suggests the possibility of their similar origin. Proof, however, cannot be established until transition from the cell nest tissue to malignant tumor tissue in the tube has been demonstrated. The author realizes this and has offered this suggestion, and only because there is as yet no established proof of the origin of these tumor types in the Fallopian tube.

There are a few questions that I would like to ask:

1. Since the tumor described originated in that portion of the tube at the mesosalpinx attachment, I would like to ask if any of the benign cell nests were found in any specimens in a similar location? In those specimens that I have observed, the cell nests are uniformly just beneath the serosa around the periphery of the tube and are not found in the mesosalpinx attachment region.

2. Are these cell nests described by the author the same as the cell groups to which the name Walthard cell nests is given?

The suggested idea of this paper deserves consideration and future efforts should be directed toward a study of the potentialities of these cell masses.

DR. JAMES R. MILLER, Hartford, Conn.—I have read the literature mentioned by Dr. Reis with great interest, for it leads me down paths which I had not previously explored. We have noted these cell balls and have observed this tendency to cyst formation. I have examined carefully the six cases of carcinoma of the tube which we have had at the Hartford Hospital, four of which have been my own, and have studied briefly nine others which Dr. Gordon Douglass kindly allowed me to review at the New York Hospital. A study of these slides leaves me with an open mind as to the possibility which Dr. Reis has suggested, but that is by no means saying that I could find many suggestions from the tubal carcinomas that would lead me to suspect the etiology in Lubeck and Brunn cell balls. Perhaps a very early specimen of tubal carcinoma may turn up which will help to decide this question. The transition which has been observed in the case of adenocarcinoma of the bladder is needed before this thesis can be considered as proved.

DR. EMIL NOVAK, Baltimore, Md.—It is difficult to evaluate Dr. Reis' paper on the mere basis of the lantern slides which he has shown, but I would have the impression that the cell nests which he has described, and from which he believes that certain cysts arise, are to be classed as Walthard islets. The latter most often appear as ovoid plaques of squamous epithelium, but they may at times be of glandular appearance. They are found more often on the tube than on the ovary. Another picture is also encountered on or near the ovarian surface which may be confused with Walthard islets. Under the influence of inflammation, marked peritoneal metaplasia may occur, with at times a heavy stratification of the cells, so that the lesion may look like a Walthard cell nest with cystic central degeneration.

So far as I know, the Walthard islets have not been suspected of giving rise to cysts, other than the occasional pseudomucinous cysts which may arise as a result of the pseudomucinous metaplasia of the Walthard epithelium which sometimes occurs. It is the Brenner tumor which is believed to have its origin from Walthard islets. Further evidence to support this view has recently been furnished by Danforth and by Ayers, who showed that the epithelial cells of Brenner tumors, and those of Walthard rests, often show an identical longitudinal coffee-bean-like grooving.

While it is not difficult to believe that certain bladder tumors arise from gland elements of urogenital origin, a similar explanation for periovarian or peritubal cysts seems to me a bit more difficult to accept, because of embryologic considerations which it would be difficult to discuss in the few seconds left me of my allotted time.

DR. REIS (Closing).—The Walthard nests seem to me to consist of squamous cells with no definite cell membrane, with pale, nonvascular nuclei that often were picnotic. None of these I have shown today has a clearly marked cell boundary, and there was no change in configuration which would make any of them coffee-bean in appearance as in the Walthard cell nests or the Brenner tumors. My experience with Brenner tumors has been very limited, but those that I have seen have had a fibrotic network with these masses of cells in the center. They are large, their nuclei pale, and in none of them were we able to demonstrate any cell membrane. While they may be related to Brenner tumors, I think some of them have been included erroneously.

I cannot presume to debate embryology with Dr. Novak, but I had the concept that possibly, as this epithelium grew upward to meet the downgoing urinary tract from above, some of these cells might have wandered just enough laterally to have been included in the downgrowth of the Müllerian duct, and might have remained over.

AMENORRHEA NOT ASSOCIATED WITH PREGNANCY IN YOUNG WOMEN*

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AMENORRHEA may be due to organic disease. Thus, it may be an early symptom in certain systemic conditions, disorders of metabolism, and tumors of the endocrine glands, or be related to pathologic changes. More commonly, an absence of the menses may be only an expression of physiologic disturbance of the glands primarily concerned with normal menstruation. Often it has been stated that menstrual function is not necessary for health. However, it should always be borne in mind, particularly if the patient is young, that amenorrhea may be a symptom of some condition that may adversely affect the health. Varying degrees of functional failure of the genital tract naturally may exist, and many patients come to the physician with menstrual irregularities. The duration and degree of such irregularities may vary within wide limits, and spontaneous remissions often occur. However, when amenorrhea has existed for a year or longer in young women, the fact should be evidence of a major derangement of function or of a disease process, and therefore merits a complete investigation.

The present paper is based on data for 94 young women between the ages of 19 and 25 years who came to the Mayo Clinic and who had not menstruated for a year or longer. They have been divided into five groups for the sake of a discussion of the conditions associated with their amenorrhea.

Group 1. Primary Amenorrhea (19 patients).—The young women of Group 1 had never experienced the menstrual function, though it is generally considered that the menses should be established spontaneously by the age of 19 years. This group of 19 patients offers a combination of developmental and functional defects that defies exact classification. Three of the 19 patients were found to have congenital absence of the vagina. Seven of the 19 patients presented normal secondary sex characteristics with no estrin or minimal amounts of this substance in the urine, together with marked hypoplasia of the uterus and atrophy of the endometrium. One of these seven patients had a large congenital cyst of the left tube and ovary that was removed. In six of the 19 patients, underdevelopment of the secondary sex characteristics was associated with hypoplasia of the uterus and endometrium and absence of estrin in the urine. The best that could be done to classify the remaining three of the 19 patients was to call them physiologic variants or tumor suspects. The values for 17-ketosteroids were elevated to more than 60 mg. in a twenty-four-hour specimen of their urine. One of them had the clinical characteristics of Cushing's syndrome, but the roentgenogram of the sella turcica and exploration of the adrenals and pelvic viscera gave entirely negative results.

Nine of the 19 patients previously had received hormone therapy for the amenorrhea without benefit. It is obvious that many combinations of develop-

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

mental and functional failure may occur which will make any functional salvage minimal. Nevertheless, each patient in this group merits careful consideration and evaluation of her anatomic and physiologic assets in order to exclude disease and to select the occasional patient who may benefit from treatment.

Group 2. Amenorrhea Associated With Tumors (7 patients).—Seven patients were found to have amenorrhea associated with the presence of tumors. Four of the tumors were located in the pituitary, one in the floor of the fourth ventricle, and two in an adrenal gland. This group of patients is small but important. Two of the seven had never menstruated and had previously received treatment for the amenorrhea; one of these was found to have a glioma on the floor of the fourth ventricle, and the other a chromophobe adenoma of the anterior lobe of the pituitary gland. These two patients did not present general or neurologic symptoms, and the lesion was evident only on roentgenographic examination. One of the total of seven patients had been treated for postpartum amenorrhea when 22 years of age. When she was seen at the clinic a year later, examination revealed a tumor of the left adrenal gland. This patient, no doubt, had little to suggest such a diagnosis early in the course of the amenorrhea, but when seen by us she presented a typical picture of Cushing's syndrome, and later died of metastasis.

These cases serve to emphasize the necessity of complete examination when a young woman presents herself with established amenorrhea. Chromophobe tumors of the pituitary and suprasellar lesions often are not associated with signs of disease of the nervous system early in their development. Assays of the amounts of hormone substances in the blood and urine will reveal the same evidence of failure of function that may occur without organic disease. The somatic changes evident in the presence of basophilic and eosinophilic adenomas of the anterior lobe of the pituitary are absent in those patients who have chromophobe adenomas and suprasellar tumors. The latter lesions interfere with the function of the anterior lobe by compression of the functioning part of the gland and not by primary alteration of function due to the new growth. The early diagnosis of the chromophobe and suprasellar tumors is often made only by roentgenograms of the sella turcica.

Group 3. Amenorrhea Associated With Anorexia Nervosa (15 patients).—Fifteen patients experienced amenorrhea in association with anorexia nervosa. Naturally, variation exists in the amount of inanition and functional failure of the pituitary and ovary in these patients. In our experience at the clinic, approximately 50 per cent of young women suffering from anorexia nervosa have associated amenorrhea.

The average weight of this group of 15 patients was 86 pounds (39.0 kg.); the least weight was 61 pounds (27.7 kg.); and the greatest, 115 pounds (52.2 kg.). The average loss of weight was 40 pounds (18.1 kg.); the greatest, 69 pounds (31.3 kg.); and the least, 19 pounds (8.6 kg.). Twelve of the 15 patients had experienced normal menstrual function prior to the onset of the amenorrhea, and in three the menstrual function previously had been abnormal. Amenorrhea had been present from one to five years.

Examination of these patients revealed evidence of marked loss of weight, the appearance of age, pallor without anemia, dryness of the skin and hair, intolerance to cold, low blood pressure, and pulse rate. They were apathetic in appearance, and presented various gastrointestinal symptoms such as fullness after eating small amounts of food, anorexia, and fairly frequently vomiting and constipation. Examination of the pelvis revealed severe atrophy of the uterus, and the external genitals had an aged appearance.

Laboratory examination did not reveal anemia. The gastric concentration of acid was sometimes low, and the glucose tolerance curve was usually flat. The basal metabolic rate was low and tended to correlate with the duration

and extent of the inanition. In this group of fifteen women it ranged from –12 to –40 per cent, with an average of –23 per cent. Microscopic examination of the endometrium revealed atrophy. Values for amounts of estrogens, gonadotropins and 17-ketosteroids in the urine were very low or, most frequently, these substances were absent. These findings indicate almost complete failure of function of the genital tract.

There is a tendency to consider the symptoms of these patients as due primarily to alteration in endocrine function, and the results of physical and laboratory examinations are adduced to prove the point. This is borne out by the fact that more than 50 per cent of this group of 15 patients had previously received endocrine treatment without benefit. The diagnosis of pituitary cachexia, Simmonds' disease, had often been made in these patients. Simmonds,[1] in his original description, showed that this condition was the result of a destructive lesion of the pituitary. Sheehan[2] expressed the belief that this lesion occurs most frequently as a result of shock and hemorrhage at the time of delivery. This author further commented that confusion appears to arise from the misconception that patients who have Simmonds' disease usually show cachexia. Fraser and Smith[3] suggested that the insulin tolerance test and estimation of the 17-ketosteroids may aid in differentiating between Simmonds' disease and anorexia nervosa.

Patients who have anorexia nervosa usually have a common starting point for their symptoms; namely, some difficulty of adjustment. They may have been overweight and initiated an ill-advised program of reduction that got out of hand, or they may have had some environmental conflict which led to a marked alteration in diet. The resulting starvation leads to varying degrees of alteration in all bodily functions, including that of the genital tract. The fact that all of these women had menstruated previously, 12 (80 per cent) having menstruated normally, would indicate that they had been endowed with essentially normal tissues.

Group 4. Secondary Amenorrhea Associated With Failure of the Ovary to Function (17 patients).—There were 17 young women in whom the amenorrhea was associated with cyclic symptoms such as nervous tension, menstrual molimina without flow, and vasomotor waves, a syndrome alluded to as the menopause when it affects older patients. The general physical examination revealed nothing characteristic. The examination of the pelvis usually revealed a uterus but little reduced in size. Seventy per cent of these patients who had ovarian failure gave a history of previous menstrual abnormality.

The basal metabolic rate was less than normal in five (29 per cent) of these 17 patients. Roentgenograms of the sella turcica gave negative results in each patient. Microscopic examination of the endometrium revealed varying stages of proliferation and occasionally subnormal secretory phases. Assays for amounts of estrogens in the urine gave varying results from none to normal or high normal amounts. High values for gonadotropins were found in 10 patients, and normal amounts were present in two patients.

The amenorrhea in these cases was considered to be primarily due to failure of the ovary to function. This, as is the case in women of the usual menopausal years, was often associated with the production of excessive amounts of gonadotropins. The values for amounts of estrogens and gonadotropins in the urine will fluctuate greatly, depending on the state of the ovarian-pituitary imbalance at the time the tests are made. These patients live in a more or less constant state of imbalance compared to the fairly even status of those patients who have amenorrhea due to failure of the pituitary to produce gonadotropins. It is this fluctuating imbalance that produces the symptoms associated with the amenorrhea in these women. There is failure of a glandular tissue living in an essentially normal environment and subjected to normal or

excessive stimulation. One may reasonably presume a fundamental fault in the ovary. The functional life of the human ovary is limited to approximately thirty-five years, but that it may be much less should be remembered.

Group 5. Secondary Amenorrhea Associated With Failure of Gonadotropic Secretion by the Anterior Lobe of the Hypophysis (36 patients).—Thirty-six patients experienced amenorrhea not associated with cyclic symptoms. This group we consider as having amenorrhea due to failure of the anterior lobe of the hypophysis to secrete gonadotropins. Thirteen of these patients (36 per cent) gave a history of abnormal menses prior to the onset of amenorrhea, compared to 70 per cent in the group primarily experiencing failure of function of the ovaries. Their general health had been considered to be normal, and the general physical examination did not reveal any abnormality. As a rule, the uterus was found to be considerably reduced in size. Roentgenograms of the sella turcica gave negative results in each case. In 20 of the 36 patients (56 per cent) the basal metabolic rate was markedly lowered, averaging –18 per cent, compared to only 29 per cent of the patients who primarily experienced failure of function of the ovaries. Twelve of these 20 gave a history of normal menses, and eight gave a history of abnormal menses prior to the onset of the amenorrhea. Gonadotropins and estrogens were either absent from the urine or present in minimal amounts. Microscopic examination of the endometrium revealed stages of poor proliferation, mixtures of proliferation and atrophy, or atrophy alone. The atrophy of the uterus and endometrium correlated with the low levels or absence of estrogens in the urine.

The lack of cyclic associated symptoms in these patients who had failure of gonadotropic function of the anterior lobe of the pituitary is owing to the lack of marked fluctuation in levels of estrogens and gonadotropins usually present in those patients previously described who experience ovarian failure. Perhaps in the 36 per cent of patients mentioned previously who experienced abnormal menses prior to the onset of amenorrhea, the anterior lobe of the hypophysis had always been at fault. It is not known whether the frequently associated lowered rate of metabolism is cause or effect.

It is difficult to explain adequately the failure of function of the anterior lobe of the pituitary in all of these patients. Some of them may be below normal in weight, but do not correspond to the anorexia nervosa group; others will be overweight, but obesity is frequently observed in women who have normal menstrual function. In the 56 per cent who were found to have lowered rates of metabolism this may serve to explain the situation, but it will not do so in the remaining 44 per cent.

Comment

No doubt there are other combinations of disease and alterations of function than those mentioned here that will result in amenorrhea. In another series of comparable size the numbers of patients in each group might vary considerably. However, these patients serve to emphasize certain considerations.

The history often gives much useful information. If the menstrual history antecedent to the amenorrhea indicates normal function, it may be assumed that normal response of tissue existed at one time in the patient's life. If, on the other hand, the patient has never experienced normal function, it may be concluded that the tissues involved were not normal, were not subjected to normal stimulation, or did not live in an environment compatible with normal function. Unfortunately, the quality of tissue responsible for function of the genital tract with which women are endowed is not uniform. When cyclic premen-

strual symptoms without flow, nervous instability, and vasomotor waves are present, one suspects that the ovary is primarily at fault. If the patient has none of these symptoms it is more likely that the pituitary has failed to stimulate the ovary properly.

The physical examination alone often gives valuable information. In the experience of my colleagues and me, atrophy of the uterus occurs more rapidly in patients with failure of secretion of gonadotropin because of the accompanying absence of estrogens. This atrophy is much less marked in patients experiencing failure of the ovary. In these cases, larger amounts of estrogens are frequently found in the urine. This is further borne out by the difference in the types of endometrium in these two groups already mentioned.

The laboratory examinations help to indicate the amount of disturbance of function of the endocrine glands. In some instances they will reveal the reasons for amenorrhea, but often they still leave the physician without an actual explanation for its occurrence, except to state that certain glandular tissues have failed or inherently lack the capacity to function normally.

I have purposely avoided consideration that the thyroid gland is primarily at fault in those instances of low basal metabolic rate without myxedema. This may be in error. The results of proper elevation of the basal metabolic rate in the treatment of obstetric and gynecologic conditions are well known from the reports of Litzenberg and Carey,[4] Haines and Mussey,[5] and others. However, the thyroid is not primarily a gland related to the reproductive system. Patients whose basal metabolic rates are considerably lower than the accepted normal frequently are seen who clinically have no general or gynecologic and obstetric evidence of physiologic imbalance. The internists have stated certain criteria for the clinical diagnosis of low basal metabolic rate without myxedema, such as intolerance to cold, dry skin and hair, and fatigability. To those may be added evidence of abnormal function of the genital tract. However, when we come to consider cause or effect, that is to say, primary hypophyseal dysfunction or primary thyroid dysfunction, a residue of 44 per cent of patients with evidence of hypophyseal failure to secrete adequate amounts of gonadotropins in the presence of normal rates of metabolism, we are left somewhat in doubt.

Amenorrhea is often considered to be static and, because the patient does not menstruate, it is considered that the functional failure remains *in statu quo*. The physiologic conditions with which amenorrhea occurs may change in the same individual during an episode of amenorrhea. Some cases fulfill the criteria for a diagnosis of failure of the hypophysis to secrete normal amounts of gonadotropins, but, while the patient is still without menses, vasomotor waves may develop and excess amounts of gonadotropins will be found in the urine. Other cases of amenorrhea will fulfill the physical and laboratory requirements for a failure of the anterior lobe of the hypophysis, but in the history will appear an episode clinically suggestive of hyperfunction of the hypophysis as a result of failure of the function of the ovary.

Conclusions

When amenorrhea occurs in young women it should be considered as a major symptom. The patient merits a complete investigation, for amenorrhea may be associated with organic disease as well as with derangements of function.

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Discussion

DR. JEAN PAUL PRATT, Detroit, Mich.—It is refreshing to listen to a discussion of amenorrhea without reference to treatment with endocrine preparations. Beginning with the purification and standardization of estrogens twenty odd years ago, a wave of symptomatic treatment was set in motion which is still rolling. Introduction of numerous natural, as well as synthetic, hormones has encouraged symptomatic treatment, so that it has, and still does, overshadow the importance of diagnosis and consideration of the patient as a whole.

One is impressed by finding 26 of the 94 patients classified as Groups 1 and 2. This raises two questions: Were the cases reported taken in series or selected, and what age limit was chosen?

Considering amenorrhea as a symptom, one looks for other symptoms or conditions to explain the amenorrhea. As Dr. Randall has shown, a complete examination of the patient is necessary. On the basis of the associated conditions, one might arbitrarily suggest three groups of amenorrhea.

Group 1 would include such structural defects as anomalies of the genital tract or tumors of the pituitary or adrenal, i.e., a real organic basis.

Group 2 might include primary amenorrhea associated with underdevelopment of primary and secondary sex characters. Many of these give a history of metabolic disturbances in earlier years. The damage was done during the developmental period. If recognized then, something might have been done to improve the development of the sex organs. If the period of growth and development has approached maturity, the possibility of developing the sex organs is small.

Group 3 could include all functional disturbances when development of the sex organs has been demonstrated by previous menstruation. This group would include most of Dr. Randall's Groups 3, 4, and 5. He has separated Groups 4 and 5 by relative amounts of gonadotropins and estrogens, as well as the relative size of the uterus and condition of the endometrium. Is the quantitative analysis of estrogens and gonadotropins and metabolic rate a sound basis for allocating the primary cause of amenorrhea to the ovary, pituitary, or thyroid? Can these glands function independently? Is the state of the uterus finally dependent upon ovarian secretion? It seems very difficult to distinguish these two groups.

Furthermore, in relation to the anorexia nervosa, the psychic factors are conspicuous and contribute to the patient getting into the state of malnutrition. Although psychosomatic factors are more difficult to measure quantitatively, their importance cannot be overlooked in any of the groups. It would seem desirable in all instances of amenorrhea, therefore, to look for the associated symptoms and conditions, to investigate the state of nutrition and environment and general health, to look for organic disturbances and treat them accordingly, to be observant of the finer shades of functional disturbance.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Review of the types of cases that are presented suggests that they were selected to emphasize certain points, rather than being taken chronologically. This is illustrated by the striking number of amenorrheas

that were associated with tumors (7 of 94 patients), two of which presented no other symptoms. It would be helpful to know the total number of amenorrheic patients from which these cases were collected. The occurrence of early tumors in the pituitary area that are silent—except for menstrual alterations—is interesting. The statistical frequency of such occurrences would add weight to their importance as diagnostic problems.

The large number of patients with anorexia nervosa (15 of the 94), suggests the selection of cases also. This group seems to present a picture of psychological maladjustment, at times associated with minor endocrinal malfunction, leading to marked dietary abuses that result in profound protein and vitamin deprivation, with ultimate female endocrinal failure. They seem to be more psychiatric or medical than gynecologic problems.

The remaining patients are divided into primary and secondary amenorrhea, with further division of the second group into those due either to ovarian, or to pituitary failure. This division is based upon symptomatology, pelvic findings, and endocrinologic studies. Analysis of the results of these studies reveals some of the many obstacles to a precise etiologic classification, and probably accounts for the broad term "failure," that Dr. Randall has chosen to use. These difficulties are most apparent in the ovarian group, with cyclic symptoms but no flow. The uteri were but little reduced in size, the endometrium showing varying stages of proliferation, and occasional subnormal secretory phases. The urine estrogen and gonadotropin assays ranged from normal to high normal, and basal rates were subnormal in 29 per cent of the patients. The uniform features are the symptoms and the uterine size, but the lack of uniformity of the other features suggests varying degrees of failure of the ovaries to perform normally, such as hypofunction, noncyclic function, or incomplete cyclic function. All of these alterations may be primarily ovarian, but one finds no proof that at least some of them do not result from pituitary or thyroid dysfunction.

In the group whose amenorrhea was attributed to anterior lobe failure, studies showed a general reduction in uterine size, with deficient endometrial changes and absent or minimal quantities of gonadotropins and estrogens. The uniformity of these results indicates ovarian hypofunction, possibly secondary to failure of the pituitary gland to perform normally. The associated subnormal basal rates in 56 per cent of the patients may be a reflection of pituitary failure, or the reverse may for some be the case, or the two may have a common etiologic background.

It is the general impression, based upon both clinical and experimental evidence, that the thyroid gland is essential to normal reproductive physiology. The role of thyroid dysfunction, whether this be primary or secondary, in functional amenorrhea has been demonstrated abundantly by its great frequency, and by the gratifying results of its treatment. In the present series both groups of the secondary amenorrheas numbered 53, and 47 per cent of these presented basal rates below minus 10 per cent. This figure is in line with the 44 per cent of subnormal basal rates in 66 patients with absent periods, as sited by Fluhmann five years ago. He was able to effect cures in 71 per cent of these, by means of thyroid therapy. No other therapeutic measure approaches these results in this condition. Steady progress is being made in the field of gynecologic endocrinology, and Dr. Randall's contribution is an important step in this progress. The cards are still stacked against us however, in the management of functional amenorrhea. It is well to play the thyroid cards to the full limit of their value, until further investigation enables us to deal better hands.

DR. HENRY C. HESSELTINE, Chicago, Ill.—Dr. Randall's title is all-inclusive. As he states, amenorrhea is a symptom and not a disease. Because his survey revealed only certain states which were associated with amenorrhea, I wish to add some of the observations made by Dr. Spear and myself upon young women with pulmonary tuberculosis.

This study was started while I was a member of Dr. Plass' department, at the University of Iowa, a number of years ago. We had a total of 134 women from 14 to 25 years of age, inclusive. Seven of these 134 patients had menorrhagia, while 65 had no menstrual cycle irregularity. The remaining 62 young women developed secondary amenorrhea. These 62 had regular menstrual cycles prior to their illness. It is evident now that after the

onset of the pulmonary tuberculosis some of these patients would miss an occasional period, while others would have an amenorrhea of three months frequently, and still others six months or longer. As far as could be determined clinically, there was no pelvic disease to explain this behavior.

The two tables list the relationship of the onset of amenorrhea, of the patient's awareness to her illness in both age groups, of 14 to 19 years, and 20 to 25 years, and correlated to the prognosis. The first table gives the respective numbers in the various categories.

TABLE I. ONSET OF AMENORRHEA IN 62 WOMEN WITH PULMONARY TUBERCULOSIS. COMPARISON OF PROGNOSIS WITH 14-TO-19-YEAR AND 20-TO-25-YEAR AGE GROUPS

PROGNOSIS	FAVORABLE			UNFAVORABLE			DEAD			TOTAL		
SYMPTOMS	FIRST	EARLY	LATE	FIRST	EARLY	LATE	FIRST	EARLY	LATE	FIRST	EARLY	LATE
Ages 14 to 19												
17	3	3	3	1	2	1	1	1	2	5	6	6
Ages 20 to 25												
45	1	9	9	0	2	2	2	7	13	3	18	24
Totals												
62		28			8			26		8	24	30

TABLE II. PER CENT OF WOMEN IN AGE GROUPS 14 TO 19 AND 20 TO 25 HAVING SYMPTOMS OF AMENORRHEA IN RELATION TO PULMONARY TUBERCULOSIS

	SYMPTOMS			
	FIRST	EARLY	LATE	TOTAL
Ages 14 to 19	5	6	6	17-27%
Ages 20 to 25	3	18	24	45-72%
Totals	8	24	30	62
	13%	39%	48%	

The second table expresses percentages of the symptoms. It will be noted that 42 per cent of the women died. However, 13 per cent had amenorrhea as the first symptom. One-half of those who had amenorrhea early could have been benefited by earlier diagnosis. There is a slight suggestion that the younger group is more likely to develop amenorrhea early.

From these findings, amenorrhea in young women may be a symptom of a serious disease elsewhere in the body rather than one of the endocrinal or reproductive systems. Accordingly, the causes of amenorrhea in young women should be considered seriously and completely.

DR. RICHARD W. TeLINDE, Baltimore, Md.—I would like to ask Dr. Randall whether he feels that cyclic therapy with estrogens and progesterone for Groups 4 and 5 has any value.

We have had great difficulty in distinguishing between those two groups. One of our cases with more than two years of amenorrhea and with marked shrinking of the uterus was placed on cyclic therapy. After several months of this she began to menstruate spontaneously and her uterus is again normal in size. We have recently curetted her and found that she has secretory endometrium, but she has failed to become pregnant.

DR. JOE V. MEIGS, Boston, Mass.—Dr. Albright of the Massachusetts General Hospital has done a lot of work on the FSH test and he believes there are three groups. The first group has the highest FSH amenorrhea due to ovarian failure, the second group has no FSH, the amenorrhea being due to failure of the pituitary gland. There is a third group who have a normal FSH, and he believes that there is a lack of luteinizing hormone. Ovulation does not take place, and ovulation is necessary to produce menstrual periods. He believes that this group is due to some failure of the hypothalamus.

DR. FREDERICK H. FALLS, Chicago, Ill.—There is another group of young women with amenorrhea not mentioned by Dr. Randall—the morphine addicts. These women have menstruated normally before they took up the morphine habit, and they became normal again after they could no longer get the drug. Therefore the amenorrhea cannot always be ascribed to an endocrinologic abnormality or to a malformation.

DR. RANDALL (Closing).—The group of patients presented here were selected on the basis of having been sufficiently investigated and followed up and, as indicated, we have to emphasize certain features of the problem of amenorrhea in the young woman. Naturally the groupings, as far as those cases with functional failure are concerned, are somewhat difficult to make.

Dr. TeLinde has raised the question of cyclic therapy. We use this a great deal in the treatment of these cases, but treatment was not mentioned in this paper for lack of time.

The question of the hypothalamus is important, of course. We talk about the pituitary being the master gland, but frequently must go beyond that to find the trouble such as, for example, the possible effect of morphine addiction, as mentioned by Dr. Falls.

Certainly one will agree with Dr. Payne that thyroid therapy is one of the best weapons we have for treating these patients. One wonders if we do not too frequently take the basal metabolic rate at its face value instead of realizing that it fluctuates greatly in many people, and that the significance of a given basal metabolic rate must be considered for the individual patient. There may be groups of women who require a lower or higher basal rate for normal function.

CONSTRICTION RING DYSTOCIA*

M. Pierce Rucker, M.D., Richmond, Va.

CONSTRICTION ring dystocia is that form of soft part dystocia characterized by the formation within the uterus of one or more bands of uterine muscle. These bands form opposite depressions of the fetal ovoid and may occur at any level. The band may entirely encircle the fetus or may extend only partially around the fetus, but in either case, so long as the ring lasts, the fetus is effectively anchored to the uterus, and there is no further progress in birth in spite of painful uterine contractions. A constriction ring (or contraction ring) is not a Bandl's ring, although the twentieth edition of *The American Illustrated Medical Dictionary* states that they are synonymous. Bandl's ring is an anatomic concept. It is located at the junction of the active contractile portion of the uterus with the lower uterine segment. As is well known, Bandl's ring ascends in obstructed labor, and the lower uterine segment becomes thinner and may eventually rupture. On the other hand, a constriction ring does not rise, but remains fixed to the fetus, and spontaneous rupture of the uterus does not occur. On account of the confusion in terminology, Rudolph suggested that the term constriction ring be revived. A constriction ring may be reversible or irreversible.

History

This condition has been known since the beginning of modern obstetrics. The early writers called it irregular contraction of the uterus. Reynolds and Newell used the term constriction ring in their textbook in 1902. William Smellie tells of being called to one of the workhouses to see a woman who had been in labor five days. The midwife told him that the woman had lost a great deal of blood the night before. The head was low in the pelvis. He first tried to deliver with the forceps, but was surprised that he did not succeed, as the head was not large and the instrument was easily introduced. "Not succeeding in the above method, I opened the head, and, in trying to deliver it with the assistance of my fingers and the blunt hook on the inside of the skull, I could not, with all my strength, bring it along. However, by extracting the occipital and one of the parietal bones, I had room to introduce my hand, so as to find with my fingers the under part of the uterus strongly girt or contracted round the neck of the fetus. This I gradually dilated: then, bringing down one of the arms and pulling at that and the shattered bones of the scalp with both my hands, I at last extracted the child with greater ease than I expected."

"In pushing up my hand to dilate, my fingers passed the mouth of the womb that was girt round the middle of the head, when I was surprised to find another contraction before the shoulders. This was the first time, I observed, that different parts of the uterus would contract so strongly, a constriction which has been commonly ascribed to the mouth of the womb." This was in 1743. Even as late as 1908, Andrews and Maxwell reported using every instru-

*Read at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

ment they had except a punch in dealing with a ring that extended obliquely in a groove of the fetus between the thorax and the flexed thigh.

Sheldon reports the following case from the Boston Lying-In Hospital. "Mrs. G., aged 35 years, gravida v, para v, was admitted at term, in active labor. The presentation was transverse, with the head in the left iliac fossa. The pelvic measurements were normal. Twelve inches of umbilical cord prolapsed soon after admission. Vaginal examination revealed full dilatation of the cervix. Internal podalic version failed because of a contraction ring. The cord stopped pulsating. Several attempts were made at high forceps delivery, all failing because of the inclination of the symphysis. Version was again attempted. As this was unsuccessful, craniotomy was performed, but the craniocast continually slipped off the skull. Version was tried a third time. After several attempts to push the head through the contraction ring, 'a snap was heard and the head was felt in the peritoneal cavity.' A laparotomy was immediately performed, and a stillborn infant, weighing 7½ pounds, was extracted. A transverse tear was found in the lower uterine segment, dissecting behind the bladder and communicating with the bladder at one point. A supravaginal hysterectomy was performed, and the ruptured area in the bladder was sutured. Vaginal and abdominal wicks were inserted. The patient, postoperatively, drained urine both by vagina and through the abdominal incision. An inlying catheter was placed in the bladder. She developed pneumonia, acute local peritonitis, and cystitis. She ran a febrile course for three weeks . . . but she finally recovered." This was in 1931.

It is evident that we are discussing a gruesome chapter of obstetrics. Perhaps for this reason it has not been discussed by this Society. The nearest approach to a discussion is Dickinson's paper (1910) in which he recommended cesarean section in a limited number of cases in which the infant is not definitely enfeebled or endangered by the length of labor, long drainage of amniotic fluid, or unskilled attempts at extraction. If the ring fails to relax under morphia or yield under complete etherization coupled with patient manual dilatation by a skilled obstetrician, a section is indicated, provided the mother be in fair condition for a laparotomy. He reported one such case. He concluded that there was a "clinical necessity of a clear formulation, or pronouncement concerning the import, diagnosis, and treatment of this condition, not only in the mind of the practicing obstetrician, but in that of the author of the textbook." The need that Dr. Dickinson voiced thirty-six years ago still exists.

I wish to discuss here 202 cases of constriction ring dystocia that I have seen in the past 43 years. These occurred in 13,575 term and near term deliveries.

Frequency

This depends somewhat upon whether the condition is looked for or not. My first 20 cases, when the recognition of the ring was practically forced upon me, occurred in 2,737 deliveries; an incidence of 0.73 per cent. I was on the lookout for the next 182 cases. These represent 1.67 per cent of 10,838 cases (Table I).

Diagnosis

The diagnosis is made with certainty upon feeling the ring with the hand in the uterus. The condition should be suspected when there is no obvious cause for the failure of labor to progress in spite of hard "pains." Phillips

says the pains are characteristic in that the painful sensation continues after the palpable hardening of the uterus has passed off. While such pains are suggestive, they are not pathognomonic. I have seen such pains when there was no ring present. Torpin has shown that, when such pains are present, there is an intrauterine pressure of some 18 mm. of Hg., whereas normally between pains the intrauterine pressure is only 5 or 6 mm. of Hg. If, upon vaginal examination, the cervix hangs loosely about the presenting part, the suspicion that a constriction ring is present is heightened.

The ring was felt in 199 cases. Three other cases were so characteristic, even though the rings were not felt, that they are included, for they illustrate a practical point in management of such cases.

TABLE I

TOTAL CASES 13,575			
Induced labor	7,354 (54.2%)	Labors not induced	6,221 (45.8%)
By amniotomy 5,111 (37.7%)			
By Voorhees' bag 2,244 (16.5%)			
Constriction rings	102	Constriction rings	100 (1.61%)
After amniotomy	73 (1.46%)		
After bags	29 (1.25%)		
Pituitrin in first stage	Total 748	Constriction ring	21 (2.8%)
Dry labors (Spontaneous ruptured membranes)	Total 483	Constriction ring	13 (2.7%)

CASE 1.—No. 4738, a 31-year-old unmarried multipara, whose pelvis and blood pressure were normal, was seen Feb. 5, 1927, in labor. The waters had ruptured spontaneously forty-eight hours previously. After a 47¾-hour labor, the cervix seemed to be fully dilated upon rectal examination. She was given a perfect sacral anesthesia. The cervix was fitting loosely about the head, which was in left occipitoanterior position. Simpson's forceps were applied and the cervix was stripped back over the head easily. Extraction was difficult. Two loops of cord were found tightly drawn about the neck. One was cut between clamps, and the cord was unwound from about the neck. I was then greatly surprised to find that I was still unable to deliver the baby, nor could I rotate it. Kristeller maneuver was ineffectual and the combined bearing down by the patient and traction on the head failed to budge the body. Five minims of epinephrine (1:1000) were then administered, and in three minutes I was able to deliver the now dead baby without difficulty. The baby was a male and weighed 8 pounds, 14 ounces. The third stage and the puerperium were uneventful.

CASES 2 AND 3.—No. 5230 and No. 5216 were similar, except that labor was induced with a bag, and there was no cord about the neck to confuse the picture. Both resisted delivery by forceps until epinephrine was given, and then the operation was easy. One baby was stillborn and the other lived. The following case is more conclusive in that the ring was actually felt.

CASE 4.—No. 15967, a 29-year-old primipara, was admitted to the Johnston-Willis Hospital May 22, 1941, having pains every five minutes. Her pelvis was normal. Her blood Wassermann was negative. Her blood pressure and urine had been normal during her pregnancy, and before that for that matter, as she was treated for closed tubes for several months before she became pregnant. After eight hours, the cervix was fully dilated and the head was on the perineum. Forceps were applied and an episiotomy was done, but the head did not descend upon traction. The forceps were removed, and the interior of

the uterus was explored. A constriction ring was found. Seven minims of epinephrine (1:1000) were administered hypodermically. The forceps were reapplied and an easy extraction was done. The puerperium was normal, and the mother and baby were discharged from the hospital in excellent condition on June 2.

Etiology

Many causes have been advanced—the administration of ergot or pituitrin, rupture of the membranes, bag, and intrauterine manipulation, and malposition. These "causes," with the exception of the administration of ergot, are represented in my cases. These are shown in Table I.

TABLE II. POSITION OF THE FETUS

TOTAL		203
Cephalic		181
ROA	18	
LOA	43	
ROP	56	
LOP	60	
Brow	1	
Face	3	
Breech		15
Transverse		3
Not stated		4

There were only 61 occipitoanterior positions in the 199 in which the position was recorded. Favorable position of the fetus occurred in only 30 per cent of the cases. There was a similar, but not so marked a deviation from normal in the pelves. The type of pelvis was recorded in 139 cases. Of these, 87 were normal, 28 were funnel, 18 justo-minor, four were flat, and two were flat rachitic. The average age of 201 patients was 28.43 years, which is a little over two years above the average for the whole series. The youngest was 17 years and the oldest 42 years of age. One hundred and thirty-four were primiparas. Something is known concerning the subsequent pregnancies of forty patients. This seems to be a small follow-up, but 13 were single and 60 were seen in consultation. The 40 patients had 47 subsequent pregnancies. The outcome of two of these pregnancies is not known. There were 8 abortions, 3 stillbirths, and 34 liveborn babies. In none of these subsequent labors was there dystocia, although one labor was prolonged. This would seem to indicate that the cause of constriction rings is a temporary one and not connected with the anatomy of the pelvis, or the uterus and its innervation. There is no common factor, not even long labor, that might be considered as a possible cause. The group on the whole presents a somewhat unfavorable selection as obstetric risks—increased age, abnormal presentations, and a larger number of borderline pelves—which fits into a working hypothesis that the ring is a fatigue phenomenon, comparable to the spasms that occur in striated muscles in runners or swimmers. Clinically, such a hypothesis is useful as a guide in the management of the case.

Prognosis

The prognosis in cases of constriction ring dystocia depends upon a correct diagnosis and the institution of proper treatment. The earlier writers reported extremely bad results: White, an infant mortality of 72 per cent, a maternal mortality of 31.5 per cent; Michael, a fetal mortality of from 40 to 86 per cent and a maternal mortality of from 20 to 33 per cent. As late as 1941, McGill reported a fetal mortality of 46 per cent and a maternal mortality

of 15 per cent. Harper, who recommended delivery from below after the ring was relaxed with deep ether anesthesia, said that the fetal and maternal mortality in his cases was negligible. Herman Johnson recently reported 105 cases in private practice with no maternal mortality and a fetal mortality of only 5 per cent.

Treatment

Constriction rings may occur at any time in the three stages of labor. When it is suspected early in the first stage, on account of the character of the pain and the lack of progress, the patient should be given morphine, demerol, or magnesium sulfate intravenously, and encouraged to sleep. Rudolph has shown that most constriction rings are reversible. If the patient is not allowed to become dehydrated, there is no reason to worry about the length of labor. After a good rest, labor is apt to progress in a more normal manner.

When the ring appears late in the first stage, or after the cervix is fully dilated, two lines of treatment are possible. One is to rest the patient and keep up the fluid intake and the electrolyte balance. Rudolph reports excellent results from this method. On the other hand, if the constriction ring can be relaxed, the baby can be delivered from below with greater safety than subjecting it to an 8- or 10-hour second stage while the ring is relaxing spontaneously. Dragging the baby through a ring that is not relaxed is not good obstetrics.

The ring can be made to relax in various ways. Beeson reports a case in which he relaxed the ring with chloroform and delivered the baby by version and extraction. There are several such cases in my series, but chloroform has failed in my hands oftener than it has helped. Harper was able to relax the rings in all his cases except one with deep ether anesthesia. My experience with ether has been similar to that with chloroform; it sometimes works, but more frequently it does not. It is interesting to note that in the 10 cases in which spinal anesthesia was used, it had no effect upon the ring. Souter reported excellent results with amyl nitrite. Barnes and Croft reported success in some cases and failures in others. Miles Phillips is of the opinion that it always works, provided enough be used. Sometimes as many as 5 ampules (5 minims) may be necessary. I have had no experience with this drug. Abarbanel's work would indicate that magnesium sulfate should be useful. I have tried it with success in suspected cases early in labor, but never as a preliminary to delivery. I believe it has merit and should be kept in mind.

Epinephrine (1:1000), administered subcutaneously in 5 to 8 minim doses, has been the most reliable relaxing agent in my experience. It was used in 150 cases. In seven, it was necessary to give a second injection, and in eight it failed to relax the ring. The action is prompt and should appear in from three to five minutes. Torpin tells me that he recently had a case in which the relaxing effect was delayed for fifteen minutes.

My cases fall into two groups; before and after the advent of epinephrine. In the first group we had no means of relaxing the ring other than anesthesia and manual dilatation. In this group there were 20 cases, with one maternal death and nine babies lost. In the second group there was no maternal death. The fetal death rate was 17.5 per cent. Eleven of the 32 infant deaths occurred in the first 23 cases.

The fatal case was that of a Negro woman, the mother of 13 children, who was admitted to St. Philip Hospital after failed forceps and version elsewhere. The ring did not relax under deep chloroform anesthesia and the fetus, which was macerated, was delivered by craniotomy. The mother did not recover from the anesthesia.

One of the cases in which epinephrine failed ended up with a Porro operation. This was a 37-year-old trained nurse, who had had an ovarian cyst

removed when she was in training. Two years after marriage and six years before I saw her, she was delivered of twins and had a postpartum hemorrhage. Her pelvis was normal and she was due by Naegele's rule the last of June, 1932. On March 4, she was admitted to the hospital on account of rupture of the membranes and was treated with bed rest, and was discharged undelivered on April 27. She began to have pains on May 9 and was readmitted. The cervix was two fingers dilated and a shoulder was presenting. A No. 5 Voorhees' bag was placed at 10:15 P.M. She was given $\frac{1}{6}$ grain of morphine, $\frac{1}{200}$ grain of hyoscine and avertin (60 mg. per kilo.). At 5:55 A.M. on May 10, the bag was removed without deflation. A knee was presenting. The patient was given ethylene, and both feet were brought down. They were shedding the skin. There was a tight ring about the thighs, which failed to relax when $\frac{1}{2}$ c.c. of epinephrine (1:1,000) was administered hypodermically. The anesthesia was discontinued. A consultant suggested that pituitrin might be tried. Accordingly, 2 minims of pituitrin were given and extraction attempted. Both legs came off below the knees. A second consultant was called in, who performed a porro cesarean section. The female fetus had a meningocele, cleft palate, and iniencephalus. The mother made an uneventful recovery and was discharged from the hospital on May 29, 1932, in excellent condition.

TABLE III. METHOD OF DELIVERY

TOTAL	203
Version and extraction	131
Braxton Hicks' version	3
Breech extraction	11
Low forceps	14
Midforceps	39
Scanzoni	2
Craniotomy	2
Porro-cesarean section	1

TABLE IV. COMPLICATIONS

Retained placenta	9	(manual removal 7)
Placenta previa	3	
Prolapsed cord	4	
Postpartum hemorrhage	1	
Eclampsia	3	
Ablatio placentae	1	
Toxemia	5	
Hydramnios	3	
Inversion of uterus	1	
Phlebitis	1	
Pyelitis	2	
Mastitis	1	
Febrile puerperium	16	
Shock	1	
Diabetes	3	
Infantile paralysis	1	

One other patient was delivered by craniotomy. She had a small pelvis and a dead baby, and had been in labor three days before admission to the hospital. The method of delivery of the 202 cases (one set of twins) is shown in Table III.

Complications accompanying these cases are shown in Table IV.

The nine cases of retained placenta with seven manual removals deserve some comment. All were due to hourglass contractions. There was no difficulty in manually removing the placenta, and no effort was made to relax the ring. Perhaps I should have given these patients another dose of epinephrine and attempted to deliver the placenta by Brandt's method, before resorting to manual removal.

Summary

Two hundred two cases of constriction ring dystocia are analyzed in regard to frequency, diagnosis, and treatment. The frequency was found to be 1.67 per cent. There is a general impression that this condition is rarer than my figures would indicate. It is quite possible that many cases are overlooked. Cases are cited to show that some difficult forceps operations may be rendered easy if the constriction ring be relaxed with epinephrine. Epinephrine was used to relax the constriction ring in 150 cases. It failed eight times. Twenty cases occurred before it was known that epinephrine would relax the ring. Of these, one mother and nine babies were lost. One hundred eighty-two mothers and 183 babies (one set of twins) were seen after the advent of epinephrine. There was no maternal death, and the fetal mortality was 17.5 per cent. Eleven of these infant deaths occurred in the first 23 cases. As experience with this drug grew, the results improved.

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Discussion

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—Dr. Rucker deserves our thanks for clearly differentiating by definition three types of uterine rings which have been discussed under so many different terms, various authors having sometimes used different terms for the same entity.

His concept of the constriction ring which he describes as a fatigue phenomenon in the presence of such unfavorable factors as primigravidity, increased age, abnormal presentations, and borderline pelves, would seem to be acceptable.

The detailed histories cited do not seem convincing. Smellie's "mouth of the womb that was girt round the middle of the head" and "the under part of the uterus strongly girt or contracted round the neck of the fetus" would seem quite obviously to be an incompletely dilated cervix and a physiologic contraction ring. Dr. Rucker makes the distinction between the constriction ring which does not change its relation to the fetus and the constriction ring which may so change its relation. But it is only under conditions of extraordinary stress that it does so. Both rings tend to adjust themselves "opposite depressions in the fetal void," and we have all, I am sure, observed the physiologic contraction ring "girt or contracted about the neck of the fetus."

There is no disposition to deny the occasional occurrence of the entity defined by Dr. Rucker as "constriction ring," definitely and objectively diagnosed by so astute an observer, by direct intrauterine palpation.

We have not, however, demonstrated Dr. Rucker's constriction ring with anything like the average 1.5 per cent frequency shown by him. His suggestion that we have overlooked many because we were not *looking for them* may be perfectly just.

There is, however, this danger. Dr. Rucker states in an earlier paper, "When, however, there is a contracted pelvis or other obstruction to labor, it is sometimes difficult to say whether the dystocia is due to the ring or the dystocia." Inasmuch as it is frequently difficult to rule out disproportion, too great concentration on the *ring*, so apt to occur concomitantly with factors of mechanical dystocia, may lead to oversight or delay in instituting management necessitated by the other mechanical dystocia.

The generally conservative attitude in management of these cases advised by Dr. Rucker is admirable. He has again drawn attention to epinephrine, which in his own hands, and that of some other observers, has been of signal usefulness.

Yet he has actually found it necessary to use some form of operative interference in 94.5 per cent of his cases; 83.5 per cent were versions or midforceps, the first especially disadvantageous under the conditions of prolonged, exhausting pathologic labor.

He has made *no* use of cesarean section, except a Porro in one case, because in another communication he properly says, ". . . cesarean section after intrauterine examination and manipulation is dangerous." This is, of course, true only of transperitoneal section. Had extraperitoneal section been employed in some of his cases complicated by mechanical dystocia, his fetal mortality of 17.5 per cent might have been materially reduced without compromise of his splendid maternal mortality of one-half of 1 per cent.

DR. NORRIS W. VAUX, Philadelphia, Pa.—The author makes a very clear-cut and distinct difference between retraction ring dystocia as described by Bandl and this specific constriction ring dystocia. Bandl, in 1875, described and defined a ring at the junction of the upper active uterine body and the lower inactive or silent lower uterine segment. This clinical observation and picture which Dr. Rucker describes so completely does not carry with it a definite pathologic course and, no doubt, in many instances has been completely overlooked or has been mistaken for a beginning incomplete or partial Bandl's ring.

However, as the author has already pictured the constriction ring as appearing in any portion of the corpus uteri in contradistinction to the retraction Bandl ring and the later relief by the administration of adrenalin, our few cases might have been of true contraction character which occurred always in long labors, in vertex or breech position, and always in those patients whose membranes had been ruptured for a long period of time. This last feature of premature rupture of membranes occurring previous to the presence of constriction ring, Dr. Rucker does not clearly specify.

In our clinic (Philadelphia Lying-In) we feel that retraction ring does not occur unless the patient has been in active labor a long time, thirty-six hours or more, some abnormality of position of the fetus and occasionally moderately contracted pelvis with a questionable fetopelvic dystocia, and that the membranes have ruptured for some hours previously.

For many years the obstetric world has been more or less confused with regard to the etiology of the retraction ring and that abnormality which embraces the anatomic, physiologic, and pathologic point of view. Schroeder, Braune, Homes, White, Fitzgerald,

and Pride have clarified a great deal of the confusion previously existing in retraction ring dystocia, but it has been to the essayist to point out further the more specific details in which retraction ring dystocia and constriction ring dystocia vary so greatly, although the frequency of either type exists in a small but very significant 1.67 per cent to 2 per cent of complicated dystocia cases. All of our cases of retraction have been relieved by rest under sedation, occasionally morphine or magnesium sulfate intramuscularly, or ether anesthesia with intravenous fluid, and when relaxation is established delivery is accomplished before the recurrence of the constriction or retraction ring. In no instance in our small series of dystocia due to this cause have we used epinephrine. There was definite increase in our stillbirth and neonatal mortality in retraction ring dystocia cases to 11.9 per cent.

Dr. Rucker gives a very timely warning not to drag the baby through an unrelaxed constriction or retraction ring but accurately to establish the diagnosis of retraction or constriction ring and to proceed with its relief with adrenalin injections. This has definitely lowered, in his hands the fetal mortality and consequently led to less maternal trauma and sequelae following delivery.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—Dr. Rucker has made the extremely important point that constriction rings may cause dystocia. He justly emphasizes the difference between such constrictions and retraction rings. They are definitely dissimilar anatomic entities. Clinically, they do offer certain comparable attributes as obstructions to spontaneous or operative delivery. Both have a common attribute in that they are primarily purely physiologic, but secondly, may become intensely pathologic.

The retraction ring may occur in one place only—namely, at the junction of the upper and lower uterine segments. It is an invariable concomitant of all labors, even when labor is precipitate. In the latter case it is merely a phenomenon of nature. Where dystocia persists, the rise of the ring and the attenuation of the lower segment may lead to pathologic rupture of the uterus.

While retraction rings are solely products of labor, this is not true of constriction rings, which may develop only in the upper segment before or during labor, and may occur only *after* the membranes have ruptured. This assertion that contraction rings are sequential to the escape of the liquor amnii is substantiated by a study of frozen sections of the bodies of pregnant or parturient women. Clarence Webster, Barry Hart, Freeland Barbour, and many others have contributed invaluable studies of such hardened and serially sectioned cadavers. In no instance have constriction rings been found in such anatomic investigations, irrespective of the length of labor, where the membranes have been intact. Where the waters have drained away, either in pregnancy or in labor, the uterus will retract upon the fetus. At first, the succulent, perhaps edematous, decidua will mold itself into every sulcus of the fetal contour. As the uterus retracts the muscularis will likewise fill every fetal depression. When the uterine muscle is in tetanic contraction, the multiple constrictions become of profound pathologic importance.

It has been twenty years since I retired, but when in practice I tried all the then putative measures for producing uterine relaxations, and found none that were of such signal value as chloral hydrate combined with sodium bromide. I doubt not that chloral still vies with all putative drugs which are alleged to relax the uterus.

DR. RUCKER (Closing).—If I have succeeded in putting across the difference between a constriction ring and a retraction ring I am perfectly satisfied.

I do want to say that it is not necessary to have ruptured membranes for a constriction ring to form. I have seen a number of cases with unruptured membranes with definite constriction rings. Also, I wish to say that the common habit of administering pituitrin when there is no progress in labor is exactly the wrong thing to do. If there is a constriction ring, a part of the uterus is already tetanically contracted and you are only adding one more insult.

ENVIRONMENT IN OBSTETRICS*

JOHN H. MOORE, M.D., GRAND FORKS, N. D.

THE difference between rural and urban obstetrics is one of environment. I have practiced "rural" obstetrics for twenty-six years. I conducted my last delivery in the home of a patient twenty-four years ago. A postpartum hemorrhage so nearly killed her that, while I was giving hypodermoclysis with a homemade normal saline solution from a 20 c.c. syringe, I vowed that if the Good Lord would let me get out of that home with a living mother I would never go back to such primitive practice. He did, and I kept my vow.

Then I started to change the environment. I am still trying to change it. I have seen the small general hospitals of my city and my state develop from the point where they had no maternity departments, no birth rooms, no nurseries, to the place where many of them have well-equipped maternity departments, modern delivery rooms, excellent nursing supervision, and good staff organizations; in brief, a proper conception of the dignity and importance of obstetrics.

This has brought me to the conclusion that, aside from the factor of environment, there is no difference between rural and urban obstetrics. But there is a tremendous difference between good and bad obstetrics! I have seen both kinds in North Dakota and both kinds in the maternity departments of our best teaching centers. I believe that we, in North Dakota, have one advantage over our professional brethren in large cities: our mistakes quickly become public property. This makes for self-analysis and, we hope, for self-improvement.

It seems to me that good obstetrics is a composite of several factors. First, there is a sound knowledge of the fundamentals. This should be obtained in our medical schools. It implies that, in addition to sound classroom instruction, the student shall have the opportunity to observe obstetrics and to take part in the conduct of pregnancy, labor, and the puerperium under the direction of competent and enthusiastic instructors. In my section of the country, this type of instruction reached its highest efficiency in the Departments of Obstetrics and Gynecology at the Universities of Minnesota, Iowa, and Wisconsin. These institutions have become recognized factors in improving obstetric practice in their neighboring states of the Midwest. They have never lost the clinical approach to the problems of the general practitioner, nor personal interest in the undergraduate student. The leadership which they have given us came, rightly, from the heads of the Departments of Obstetrics and Gynecology. They imbued their staffs with an interest and enthusiasm for teaching clinical obstetrics that has paid dividends in a decreasing maternal mortality.

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

Our nearest neighbor in North Dakota is Minnesota. During the formative years of our maternal welfare program, we had the practical and sympathetic help of Doctor Jennings C. Litzenberg. He gave us courage and criticism in large measure. He came to help us. His leadership was spiritual as well as intellectual. To us his name became synonymous with good obstetrics. We can pay him no finer tribute.

As a country doctor, I would like to see an intensification of the teaching of the fundamentals. I have talked with many recent graduates in medicine. Many of them have admitted that their clinical training in obstetrics has been inadequate. If this condition has been brought about by war, it may correct itself in another medical generation; if, however, it is the result of too much theory and not enough practice in the impressionable undergraduate years, we need to revamp some of our teaching. I am old-fashioned enough to believe that the chief function of a medical school is to prepare students to practice medicine.

The second factor in good obstetrics is a sustained professional interest. In a rural state, environment becomes important in developing it. A lone doctor in a community must not be allowed to become a lonely doctor, or else both he and his patients will suffer. The doctor must have postgraduate opportunities made available to him in such a manner that he can keep abreast of current thoughts and trends in obstetric practice without too long absence from his practice.

Finally, as a third factor in promoting good obstetrics, I would emphasize the importance of integrating all of the agencies which have for their object the improvement of obstetric practice under the leadership of the medical profession.

In 1935, we formed the North Dakota Committee on Maternal and Child Welfare. It was appointed as a special committee of the North Dakota State Medical Association and, one year later, won recognition as a standing committee. It is predominantly a committee of general practitioners. It is the advisory committee to the North Dakota State Health Department in matters of maternal and child welfare. Thus, in this important field, the most cordial relationships have been established and maintained between the State Health Department and the State Medical Association.

In 1935, we had a maternal mortality rate in North Dakota of 55 per 10,000 live births. We called the committee to an immediate attack on this problem. We divided the "fatal triad" among our membership, and requested them to prepare practical papers on infection, toxemia, and hemorrhage for presentation before the district medical societies of our state. We then obtained invitations from the thirteen district societies to present these papers before them, and we were careful to assign our speakers to societies other than their own on the well-established principle that "a prophet is not without honor, save in his own country."

In 1936, we recommended to the State Health Officer that funds be made available to bring outstanding clinicians to the state to conduct obstetric and

pediatric seminars at six convenient centers. Highlighting these all-day seminars were the round table discussions that featured each. The committee obtained splendid cooperation from the officers of the various medical societies in making local arrangements for them and in advertising them to their members. We continued this type of instruction through 1938. A recent questionnaire regarding them resulted in a request from a majority of our physicians that they be renewed.

In 1937, we asked the Maternal and Child Hygiene Division and the Division of Vital Statistics of the State Health Department to begin an analysis of each maternal death that occurred in North Dakota. Only two stipulations were made by the committee: The name of the attending physician and the place of death of the patient were to remain anonymous as far as the data, submitted to the committee, were concerned. Trained physician investigators from the State Health Department have conducted these investigations, and they have had the full cooperation of the medical profession. From an analysis of the yearly surveys, the committee has been able to discover certain trends and recommend certain corrective measures which we feel have been of benefit to the physicians and their obstetric patients. Two items only will be mentioned. The committee recommended a uniform summary record for all hospitals admitting maternity patients. This record is now in use throughout the state. We recommended consultation before all cesarean sections. This consultation rule is being adopted.

In 1938 the Maternal and Child Welfare Committee sponsored the founding of the North Dakota Society of Obstetrics and Gynecology. It began with nine members and now has 36, seven of whom are diplomates of the American Board of Obstetrics and Gynecology, three more limit their practices to those specialties, and 26 are general practitioners. We cannot be accused of specialist domination! The Society has flourished since its inception. It has had excellent program meetings and has always worked hand in hand with the State Medical Association.

In 1938, I suggested to the Maternal and Child Welfare Committee that postgraduate education for North Dakota physicians be broadened to include short courses in residence at near-by teaching centers. This proposal had the enthusiastic support of Doctor William A. O'Brien, Director of the Center for Continuation Study at the University of Minnesota, and the North Dakota State Health Department furnished the stipends for ten North Dakota physicians to attend the first course. The physicians were selected by application through their district medical societies. There were sixty applicants for the ten places. The first course was given at the University of Minnesota in May, 1939. The plan was continued and enlarged. Through the splendid cooperation of Doctor Everett D. Plass, the Department of Obstetrics and Gynecology of the University of Iowa agreed to take our physicians for their bedside teaching course in obstetrics. To date, over 150 North Dakota physicians of the 360 in the state have availed themselves of postgraduate instruction in these courses at the University of Minnesota and the University of Iowa, and the requests for this type of instruction have not diminished. We acknowledge,

with deep appreciation, our debt to these two teaching centers for having made this most practical instruction available to our physicians.

In 1940, we had reached a maternal mortality rate of 17 per 10,000 live births, and we felt that some improvement had been made. Then the rate began to rise. It was 26 per 10,000 live births in 1941, 25 in 1942, 29 in 1943. In 1944 it had fallen to 18, and the provisional rate for 1945 is 11 per 10,000 live births. Statistically, this rise and fall within rather narrow limits does not seem important to me. But it did not seem important that our rate of 29 per 10,000 live births in 1943 coincided with the year in which deaths from obstetric hemorrhage went into first place, ahead of infection and toxemia. An analysis of the individual case summaries of maternal deaths from hemorrhage during that year showed that two factors were chiefly responsible for the rise: (1) injudicious operative obstetrics, and (2) inadequate blood substitutes.

The first factor is not limited to North Dakota! It is nationwide. It first began when panic seized the first obstetrician in the presence of dystocia, it increased under the false assumption that modern operating rooms had made cesarean section the best way out of obstetric difficulties, and it was further encouraged by the false sense of security provided by sulfonamide therapy and, later, penicillin. The end is not yet. Intensive education is still needed to impress present and future medical generations with its dangers.

The second factor, inadequate blood substitutes, was a particularly important one in North Dakota. I read several case histories of deaths from hemorrhage, ascribed to placenta previa. In four of these cases in one year and in widely scattered areas, blood donors had, eventually, been obtained; but not before the irreversible reaction had set in. In Grand Forks we had been working on a pooled liquid plasma project. One of my partners, Doctor R. O. Goehl, and the Director of the Division of Laboratories of the State Health Department, Mr. Melvin E. Koons, had shown the safety of this product for local use. The product they prepared was highly satisfactory when kept under proper storage conditions, but we soon came to the conclusion that it would not be practical or safe for statewide distribution.

Mr. Koons set to work to see if we could manufacture dried human plasma, and we set out to get a bill through a special session of the North Dakota Legislature in February, 1944, authorizing the establishment of a State Plasma Bank in the Public Health Laboratory at the University of North Dakota. Both projects were successful, and an initial appropriation of $10,000.00 was granted. The University of North Dakota added additional funds and supplied the space necessary for the plasma bank. The first dried human plasma had passed its tests by August 27, 1944. It seemed interesting to have data available to show the results of the first year of operation. I am indebted to Mr. Koons for the tables:

Thus, it will be seen that about 18 per cent of the patients who received North Dakota-made plasma during the first year of operation of the plasma bank were obstetric patients.

TABLE I. THE USE OF PLASMA IN OBSTETRIC PATIENTS FROM AUGUST 27, 1944, TO AUGUST 27, 1945

	PATIENTS	UNITS
Ectopic pregnancy with severe hemorrhage	9	16
Placenta previa	16	27
Postpartum hemorrhage	64	92
Abruptio placentae	2	2
Cesarean section	3	8
Abortion	18	22
Vaginal bleeding	2	4
Total	114	171

TABLE II. THE EXTENT TO WHICH PLASMA HAS BEEN USED THROUGHOUT NORTH DAKOTA DURING THE FIRST YEAR OF OPERATION OF THE PLASMA BANK

Total communities in which one or more units of plasma has been used	38
Total number of counties in which plasma has been used	32
Total reports received on units of plasma to date	1,250
Total number of patients receiving plasma	663

TABLE III. DISTRIBUTION OF PLASMA

Hospitals	44	
Physicians	31	
Drugstores	3	
Total depots	78	
Total number of counties in North Dakota*		53
Total number of counties having plasma		49
Counties with no hospital or physician		3

*One total county is Indian Reservation.

TABLE IV. TOTAL COST OF PROGRAM

Total cost of program to date	$26,572.14
Cost per unit of plasma since the beginning of the program	12.56
Estimated cost per unit for the coming year	
Minimum	2.75
Maximum	3.00

The distribution of the plasma throughout the state is of interest because it again calls attention to the factor of environment. Table III gives that distribution.

The total cost of the program during its first year of operation and the anticipated cost of plasma in the future are of interest and appear in Table IV.

I have used the plasma bank as another illustration of how environment can be changed with resultant good, not only to the practice of obstetrics, but to the general practice of medicine and surgery.

Our next and, I believe, our most far-reaching and important step in changing the environment will be the establishment of a four-year medical school at the University of North Dakota. We were successful in getting the last session of the North Dakota Legislature to pass an enabling act, authorizing the establishment of a Medical Center at the University of North Dakota. I visualize the integration of a number of the established hospitals throughout the State into a teaching program with the University and giving the medical students in the University firsthand insight into the problems of medical prac-

tice in North Dakota by bringing them into close teaching contact with a number of the excellent practitioners throughout the state. In this way we feel that our medical students and young graduates would come to love North Dakota, even as I have come to love it, by intimate contact with its people. This is not a program for a day or for a year, but it is a long-range program that will have both tears and triumphs along its way.

We have come far enough along the way in medical education in North Dakota to know that in obstetrics, for example, our physicians are eager for the best. They want postgraduate education made more readily available to them and this a Center, such as I have indicated, can provide. I have seen how well the all-too-few opportunities that have been provided for postgraduate instruction in obstetrics have been utilized in the saving of the lives of mothers. We have only begun.

Discussion

DR. GEORGE W. KOSMAK, New York, N. Y.—Dr. Moore's contribution exemplifies the progress in obstetrics in his locality through the medium of individual efforts by conscientious and enthusiastic practitioners, by efforts stimulated from within and not from without. The presentation discloses, moreover, that simplicity of procedure may be equally effective in producing results as the more elaborate and costly methods by which the graduates of our medical schools and many of our hospitals have become infected. It should still be possible to conduct satisfactory deliveries under ordinary circumstances even in the homes, in areas where hospital facilities are not readily available, or where poor hospitals constitute a danger in themselves.

Naturally enough, Dr. Moore stresses the desirability of hospital deliveries, but, with proper preparation, a home delivery can be made almost equally satisfactory, if perhaps less convenient for the physician. Of course it is a matter of environment, and the environment must be made safe. That depends on the doctor, and the nurse, and the family. Perhaps we can never reach that stage of perfection when there will be provided universal, adequate, and competent hospital care, and in the meanwhile we may have to improvise. There may be areas where medical facilities are inadequate, but there is still an aid in the properly supervised trained nurse-midwife, to whom, however, Dr. Moore does not refer.

Dr. Moore stresses the importance of postgraduate training of the physician to keep him up to date. My own observations have convinced me that we need less of the display of modernity than we do of stressing such elementals as the anatomy and physiology of pregnancy and labor, as well as the necessity for aseptic technique, adequate diagnosis of the normal, and proper appreciation of the abnormal.

The postgraduate lecture seminars of many of our State Medical Societies feature too largely, in many instances, the academic, the laboratory, the exceptional, the abstractly scientific phases of obstetrics. The practicing physician may believe that he needs "brushing up," but it is doubtful, to me at least, whether an abstruse evening lecture by a visiting specialist will afford him much satisfaction or actual benefit. I rather lean to and have advocated in my own state a visit of from a few days to perhaps a week to a teaching center with attendance at clinics, in wards, in the delivery room, places where he comes into contact with the actual patients. For the younger men, the brief residencies, to which Dr. Moore refers, are also most desirable, provided they are not affected too much by the "fancy" obstetrics witnessed and attempt them when they return. In my belief, it is the obstetric elementals which should be impressed.

I therefore agree with much of what Dr. Moore presents in his paper, and his suggestions might well be applied elsewhere. The maternal death rate in this country has declined in an extraordinary manner, and this is due, in my belief, to the analysis of its own work by the profession in the various study committees which have been developed over

the country. But we must not stop with achieving a lower mortality rate; the avoidable complications and accidents, and morbidity likewise must be reduced.

Dr. Moore stresses environment as a factor in the successful conduct of obstetric procedures. In large measure this is true, but no matter what the material environment may be, the actual criterion of success is the knowledge and ability which reside in the doctor who has assumed the responsibility of bringing the woman successfully through her pregnancy and labor. He in a sense is the one who creates the environment. I feel that Dr. Moore and his group should be highly commended for their efforts to inculcate in their region an appreciation of good obstetric care.

DR. RUDOLPH A. BARTHOLOMEW Atlanta, Ga.—Poor environment in obstetrics, as so well pointed out by Dr. Moore, is not so much a matter of geography as it is a matter of lack of physical equipment and obstetric skill and judgment. It is not enough to supply modern physical facilities, for these, in the absence of obstetric conscience, skill, and judgment actually tend to worsen obstetric morbidity and mortality through temptation to use unwarranted operative procedures.

Step by step, in logical sequence, the essayist has traced the essentials of good obstetrics, from thorough basic undergraduate training to continued postgraduate instructions through the years of practice, to sustain interest and help the practitioner reach greater obstetric proficiency.

In lieu of compulsory periodic renewal of licensure, which some have advocated to insure that practitioners keep abreast of progress in medicine, it would seem far better to provide facilities for compulsory refresher postgraduate instruction to accomplish the same end.

The success attending the writer's efforts to integrate all agencies, State Health Department, lay and professional, having as their objective improved obstetric care, is reflected in the lowered infant and maternal mortality rate.

It occurs to me that the State Boards of Health could furnish a much needed service by appropriating funds to subsidize free consultation by long distance telephone, for practitioners confronted with obstetric problems of emergencies. Well-qualified obstetricians, preferably members of the American Board of Obstetrics, could be appointed to serve as consultants. The state could be divided into districts, each of which could be served by a consultant and his alternate for a certain period of time.

It is my belief that practitioners would welcome such a service, and that much good could be accomplished in directing the proper management of the case and benefit both the patient and the practitioner.

Dr. Moore's paper brings home to us the fact that whatever is of practical value in original research, or papers presented before our special societies, must depend for its dissemination and ultimate benefit on facilities such as he has pioneered in North Dakota.

DR. MOORE (Closing).—As to the question of the nurse-midwife, in 1940 our physicians delivered 94 per cent of the obstetric patients in North Dakota, and in 1945 they delivered 99 per cent of them. Thus far we have not had to resort to nurse-midwife deliveries in very many cases. If our decline in the number of physicians continues, we might have to use more midwives than we have in the past.

ENDOLYMPHATIC STROMAL MYOSIS*

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(From the Departments of Obstetrics and Gynecology and Pathology of the University of Toronto)

THIS paper is a report of a clinical and pathologic study of seven unusual uterine tumors arising from the endometrial stroma. Five of these tumors were received from the gynecological service of the Toronto General Hospital, one from the Wellesley Hospital, Toronto, and one from the St. Catharines General Hospital, St. Catharines, Ontario. The tumors are identical in most of their histologic and pathologic characteristics. They are composed of cells which closely resemble the cells of the endometrial stroma. They spread by direct extension between bundles of uterine muscle, along perivascular and perilymphatic tissue spaces, and within the lumen of both vascular and lymphatic channels. These histologic characteristics identify them as similar to neoplasms that have been described by Casler,[1] Frank,[2] Goodall,[3] Miller and Tennant,[4] and Robertson and his co-workers.[5]

In 1919 Casler, the first to report this type of neoplasm, described it as "a unique diffuse uterine tumor, really an adenomyoma with stroma but no glands." In his case the tumor obviously arose from the endometrial stroma and had diffusely invaded the uterine wall in a manner similar to adenomyoma. In 1932, Frank reported three cases similar in histologic appearance to the one of Casler, but exhibiting a spread almost completely confined to peri- and intralymphatic channels. Frank described the close resemblance between the tumor cell and the endometrial stroma cell, but could not demonstrate a direct continuity between the endometrium and the tumor. In 1937, Goodall reported fourteen cases presenting gross and microscopic features, which closely allied them to the cases previously reported by Frank and Casler. He suggested the name "stromal endometriosis" for these tumors. Since 1937, nine more cases have been reported, three by Miller and six by Robertson.

These authors have all described their cases in detail. Nevertheless, the rarity of the lesion, its uncertain malignancy, and unusual pathologic characteristics would seem to warrant this present report. The first of our seven cases was encountered in 1933, the last in 1942. The original pathologic diagnosis in all cases was endometrial sarcoma.

Pathology

In all cases, the uterus contained one or more tumor masses, which, depending on their size, situation, and number, caused regular or irregular enlargement of the uterus. The largest uterus contained multiple tumors and measured 24 cm. in its widest diameter (Fig. 1). The smallest contained a single tumor

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

measuring 6 cm. in diameter. These tumors were subserous and interstitial in situation, and in all but two cases formed, as well, varying sized sessile and polypoid tumors, which partially filled the endometrial cavity (Fig. 2). They were nonencapsulated, of soft brainlike consistency, and on section were faintly yellow in color and of homogeneous, velvety texture. Small cystic spaces filled

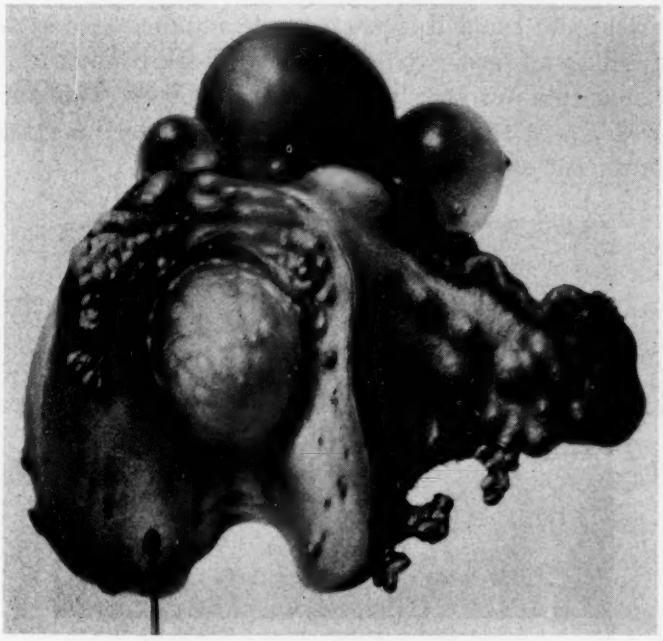

Fig. 1.—Case 1. Uterus enlarged by multiple tumor masses. The broad ligament lymphatics are nodular and distended with fingerlike processes of tumor which are protruding from the cut vessels. The probe indicates a distended lymphatic in the uterine wall out of which tumor has been pulled.

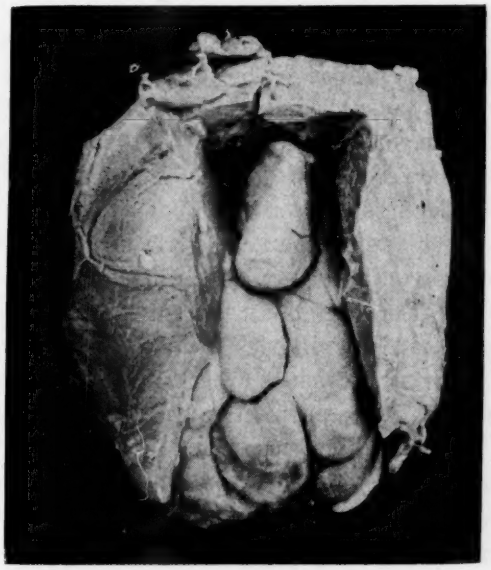

Fig. 2.—Case 7. Uterine cavity filled with a polypoid tumor mass.

with clear fluid were present in the larger tumor masses in three separate specimens. In one specimen extensive interstitial hemorrhage had occurred into the largest tumor which filled the endometrial cavity. Radiating out from these large tumors were cords and islands of tumor tissue infiltrating the myometrium. For the most part, they appeared to lie in vascular and lymphatic channels (Fig. 3). They stood out prominently above the cut myometrial surface of the fresh specimen, and could be squeezed out or pulled free as slender worm-like strands of rubbery tissue. Extension beyond the boundaries of the uterus into the broad ligaments was grossly evident in five cases. This was particularly noted in the areas about the uterine vessels where fingerlike strands of tumor protruded from the cut vessels.

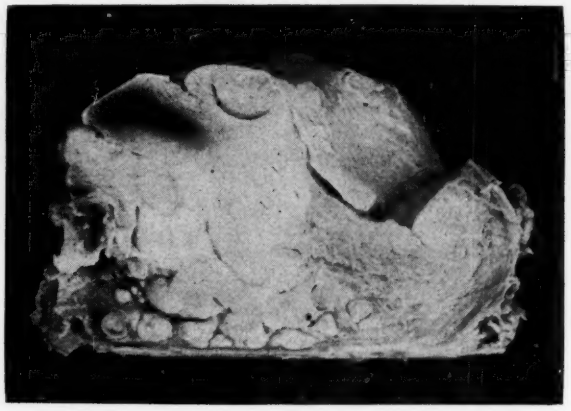

Fig. 3.—Case 7. Sagittal section of uterus in Fig. 2 showing infiltration of the posterior wall of the uterus by cords of tumor, the majority of which are in lymphatic channels.

Microscopically, these tumors were composed of cells which for the most part closely resemble the endometrial stromal cell of the late proliferative phase. The cells were remarkably uniform in size, shape, and staining qualities. In some areas, a fibrouslike appearance of the tumor cell was noted, a change similar to that which is frequently observed in the stroma of the endometrium in endometrial polypi. In one specimen, that portion of the tumor which partially filled the endometrial cavity showed a moderate degree of anaplasia hyperchromatosis and an occasional mitotic figure. Areas of edema, myxomatous-like degeneration, and the formation of varying sized cystic spaces were also observed. A most characteristic microscopic feature of the tumor is the presence of numerous thick-walled blood vessels resembling the spiral arteries of the endometrium. The vessels varied from small capillaries to thick-walled muscular arteries, and were strikingly evident in all sections (Figs. 4 and 5). The large tumor masses were not encapsulated and were in direct contact with the uterine wall, forming a slightly irregular tumor myometrial junction similar to that of the normal endometrium. A varying degree of myometrial hypertrophy was evident in only three specimens, and in none was it present to a marked degree.

The myometrium was invaded by broad and slender cords of tumor extending between muscle bundles and along perivascular and perilymphatic tis-

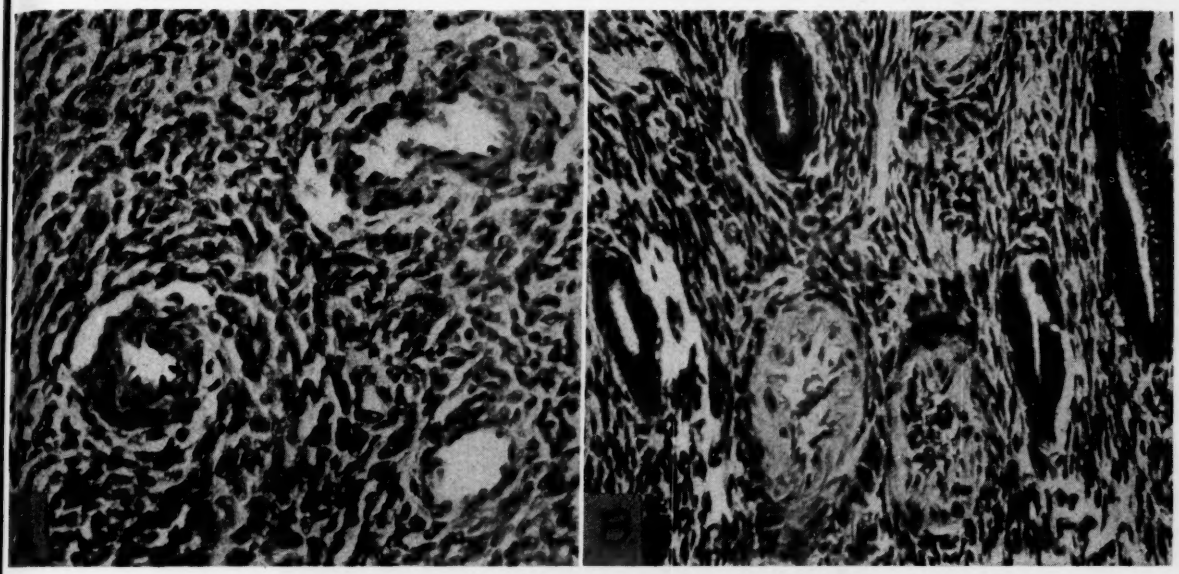

Fig. 4.—Case 6. *A*.—Section showing the thick-walled blood vessels which are a strikingly constant feature of the tumor. Comparison with the normal endometrium, section *B*, reveals the close resemblance between the cells and blood vessels of the tumor with the stromal cells and blood vessels of the normal endometrium. (×230.)

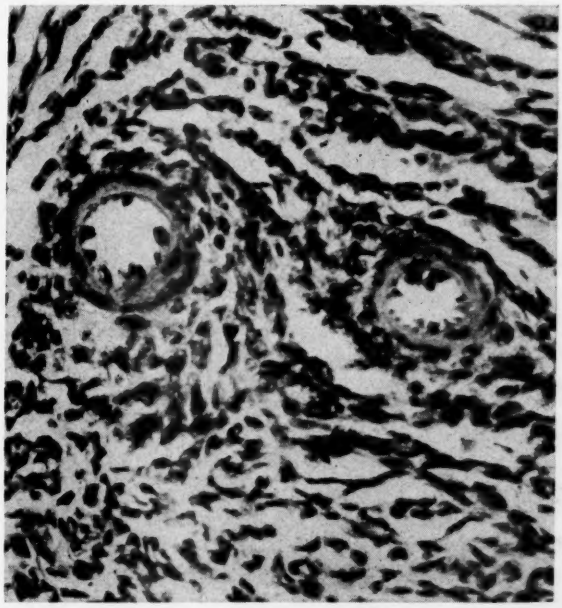

Fig. 5.—Case 6. Section of tumor removed from a lymphatic channel. (×320.)

sue spaces (Fig. 6). These strands of tumor were frequently seen pushing their way into lymphatic channels while still covered by intact endothelium (Figs. 7 and 8). In most areas, however, they appeared as masses of tumor tissue lying free in lymphatic spaces (Fig. 9). Invasion of blood channels

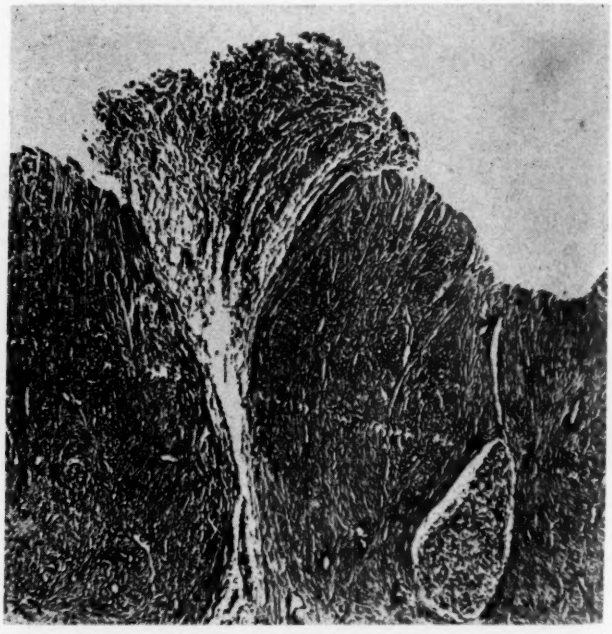

Fig. 6.—Case 3. This section shows tumor growing between muscle bundles and within the lumen of a lymphatic channel (×46.)

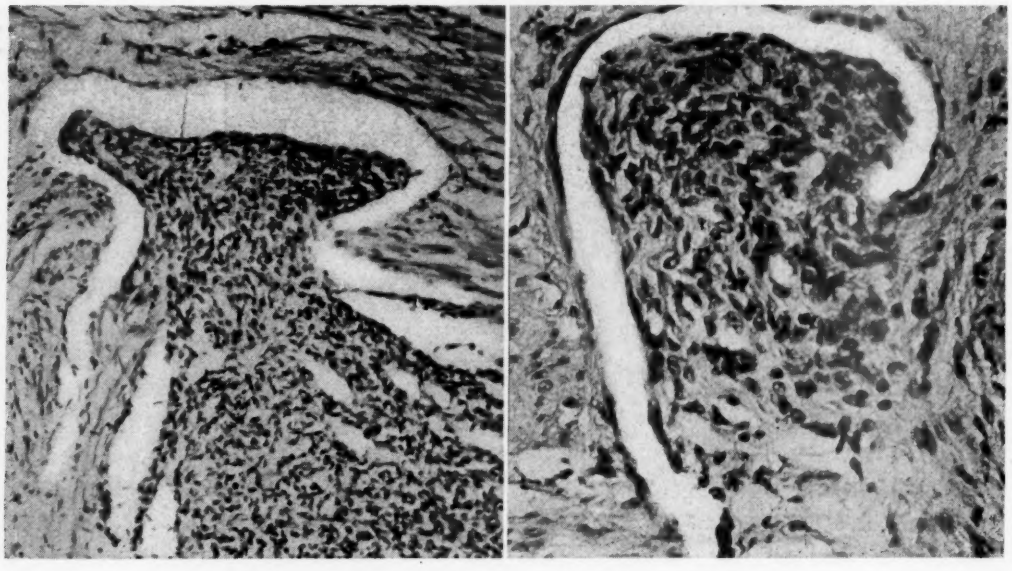

Fig. 7. Fig. 8.

Fig. 7.—Case 3. Tumor growing between muscle bundles and into a lymphatic vessel. (×120.)

Fig. 8.—Case 6. Tumor bulging into a lymphatic vessel but still covered by intact endothelium. (×320.)

could be demonstrated with less frequency than invasion of lymphatics, due in part to the difficulty of differentiating between capillaries and lymphatics. Vascular invasion, however, could be established readily when the invaded vessel was thick-walled or contained a sufficient number of red blood cells to identify it as a blood vessel (Fig. 10). The lymphatics and wall of the Fallopian tube were infiltrated in two cases, and in one of these the subserous venous channels also were distended with tumor (Figs. 11, 12, and 13).

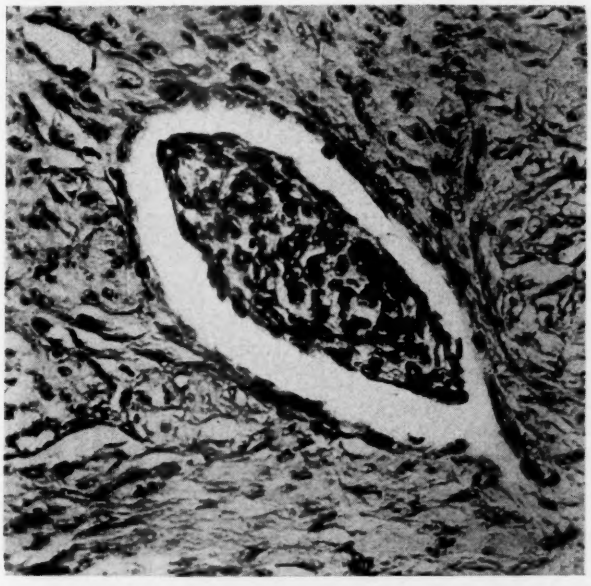

Fig. 9.—Case 6. Tumor within the lumen of a lymphatic channel. (×480.)

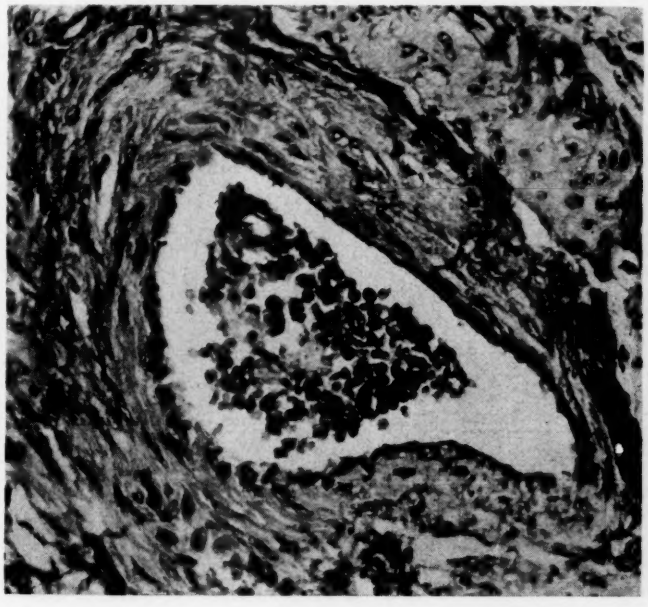

Fig. 10.—Case 3. Tumor within the lumen of a blood vessel. (×300.)

Direct continuity between the endometrium and the intramural tumor was evident in five cases. In two cases, despite a diffuse involvement of the posterior wall of the uterus, no such continuity could be shown. In both of these cases the tumor could be traced within a few millimeters of the basal layer of the endometrium, yet, despite multiple sections, direct continuity could not be established.

Fig. 11.—Case 3. Section of Fallopian tube showing infiltration of its wall by tumor. The lumen of the tube is at the lower right of the photomicrograph. Small capillaries above the tubal lumen are filled with tumor, and to the left a large mass of tumor pushing into and dilating a lymphatic channel is evident. (×20.)

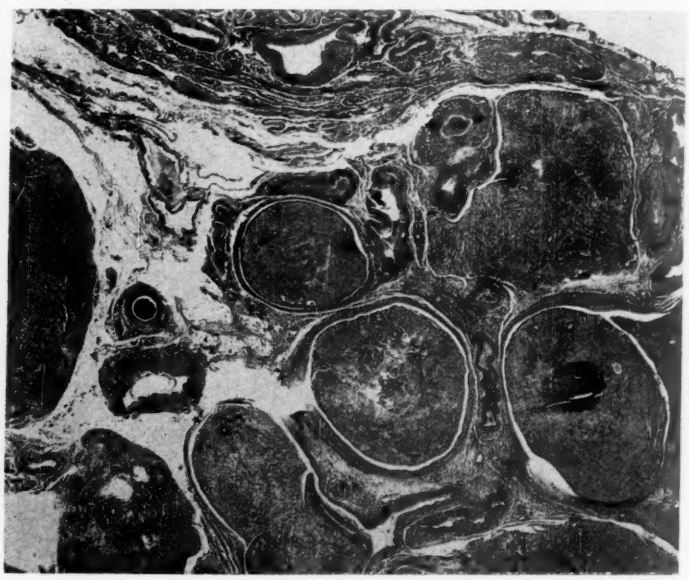

Fig. 12.—Case 1. Lymphatic vessels of the broad ligament filled with cords of tumor. (×20.)

A great number of sections from all seven cases were examined, and in only one instance were endometrial-like glands encountered in the intramural or subserous portions of the tumor. These were found in a block cut from a large subserous tumor in Case 6. They comprised a clump of three typical endometrial glands of the proliferative phase. It is possible that they arose from invaginations of the serosal covering in the subserous tumor by a process of metaplasia of the serosal cells. Glands were occasionally encountered near the surface of the sessile and polypoid tumors in the endometrial cavity. These probably represented remnants of the endometrium, which originally had covered the surface of the polypus.

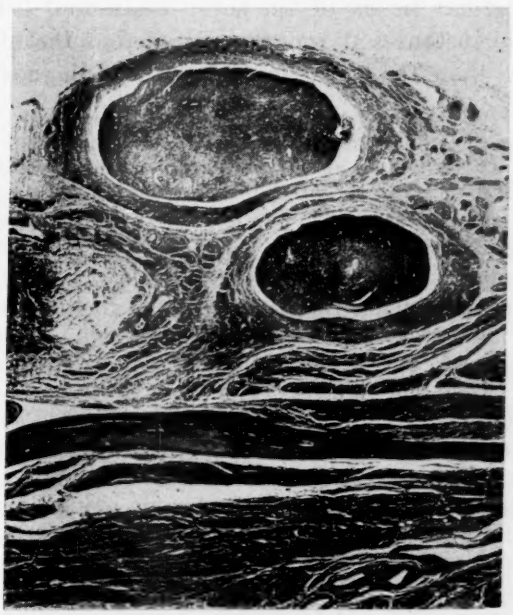

Fig. 13.—Case 2. Tumor within the lumen of two subserous veins. (×20.)

Sections were stained to demonstrate reticulum using Laidlaw's silver stain. They showed a basket-weave network of the reticulum surrounding the individual tumor cell similar to the reticular pattern of the endometrial stroma.

Clinical Features

An analysis of the clinical histories of these cases failed to reveal symptoms or signs that could be considered distinctive for this type of tumor.* In one case, menstruation was undisturbed. In the remainder, bleeding was irregular and profuse. The blood loss was quite severe, as in five of these the hemoglobin estimation was less than 50 per cent. In one case, the symptoms due to the presence of the tumor were masked by a tuberculous salpingo-oophoritis and pelvic peritonitis. The age of the patients varied from 28 to 45 years. Parity was widely varied, from para 0 to para vii.

*The clinical features of the cases are summarized in Table III.

TABLE I. AGE AND PARITY

CASE NO.	AGE (YEARS)	PARITY
1	32	3
2	37	2
3	44	7 (13 abortions)
4	47	2
5	28	0
6	45	4
7	45	0

The essential finding on examination was enlargement of the uterus. This enlargement was irregular in six of the seven cases, and led to a diagnosis of fibromyomas. In two instances it was recognized that the uterine tumors were of softer consistency than the usual myoma, and a diagnosis of degenerating fibroid was made.

All seven cases were subjected to bilateral salpingo-oophorectomy and hysterectomy. The findings at the original laparotomy in three cases did not excite the suspicion of the surgeon that he was dealing with an unusual type of uterine tumor. In the remaining four cases it was immediately evident that a most unusual lesion was present. The broad ligament lymphatics were enlarged, ropey, and hard. In one case extension could be palpated in the perivascular lymphatics of the left ovarian artery up to the renal vessels. The infundibulopelvic ligaments were thickened, and when clamped and cut, wormlike masses of tumor squeezed out between the clamps. The same thing again occurred when the uterine vessels were severed and the uterus amputated. In these four cases the condition appeared to be beyond the hope of surgical cure and the operation was completed as a palliative measure. The uterine tumor masses were covered by smooth glistening peritoneum, and there was no evidence of secondary peritoneal implantation of tumor cells. Peritoneal adhesions were absent in five cases. In two cases adhesions were numerous, but in one were due to previous laparotomy for ruptured appendix, and in the other to tuberculous salpingitis. There were no findings suggestive of endometriosis.

One patient originally had a supravaginal hysterectomy and left salpingo-oophorectomy. Following the pathologic diagnosis of sarcoma of the uterus, a second laparotomy was performed, and the remaining tube and ovary and cervix were removed. The patient with tuberculous salpingitis had, in all, four laparotomies. At the first, the tuberculous adnexa only were removed, due to the poor general condition of the patient and operative difficulties. The uterus, at this time, was thought to contain ordinary fibroids. One year later, due to uterine bleeding, a second operation was performed and the uterus was removed. Two and a half years later a recurrent tumor was removed from the retroperitoneal cellular tissue. Eight months later, and four and a half years after the original operation, a fourth laparotomy was performed for large bowel obstruction due to another local recurrence. A colostomy was done. The patient died five months later. Unfortunately, a postmortem examination was not permitted.

Five of the seven patients received postoperative high voltage x-ray therapy. Three of these received high voltage at 400 kilovolts; 100 cm. distance; 30 treatments through five pelvic ports, two anterior and three posterior, to 1,800 R per port. In addition, one of these five patients received 15 treatments through the vaginal cone to 3,000 R. In the remaining two cases, high voltage at 200

kilovolts, 50 cm. distance, was employed. One received 1,200 R per port, the other 1,600 R and, in addition, 1,100 R through four abdominal ports to cover the whole abdomen.

The follow-up record for all cases is shown in Table II, and reveals that six patients are alive and well, and one has died from recurrent disease.

TABLE II. FOLLOW-UP RECORD

CASE NO.	DURATION OF FOLLOW-UP (YEARS)	STATUS
1	9	Alive and well
2	9	Alive and well
3	7	Alive and well
4	7	Alive and well
5	3	Alive and well
6	6	Alive and well
7	5	Dead

Discussion

These tumors possess characteristics which make them difficult to classify as either benign or malignant. The tumor cell is a well-differentiated mature type of cell, showing an absence of anaplasia hyperchromatosis and mitotic figures, all of which denote benignancy. The presence of thick-walled blood vessels, a strikingly constant feature of the neoplasm, suggests slow growth, a characteristic usually associated with benign tumors. The manner of invasion of the uterine wall by pushing between muscle bundles and along perivascular tissue spaces without actual destruction of muscle resembles the myometrial invasion of adenomyosis rather than sarcoma. The widespread invasion of lymphatic channels and, to a lesser extent, of blood vessels, however, is an attribute of sarcoma, and sets the stage for the occurrence of distant metastatic growths that are characteristic of malignant neoplasms. That distant metastases have not been an accompaniment of these tumors is surprising. The tumor, when pulled from lymphatic channels, is not in the least friable, but of rather rubbery consistency, a characteristic that may explain the absence of embolic metastases.

It was grossly evident in six cases that surgical removal of the tumor had been incomplete, yet five of these patients are alive and well after six to nine years. This failure of the tumor left in situ to continue its growth is difficult to explain. Four of the five patients received high voltage x-ray and one did not, yet all have survived to the present. The mature, well-differentiated tumor cell would not ordinarily be considered as particularly radiosensitive. Goodall, who considers the lesion a type of endometriosis, believes that its growth is dependent upon estrogen stimulation from the ovary. All of our cases had bilateral oophorectomy. Yet, in one the tumor continued to grow, and the patient eventually died from massive local recurrence. Of Goodall's two fatal cases, one had bilateral oophorectomy, and the other received radium and high voltage x-ray therapy that ordinarily would destroy the secretory function of the ovaries. The abundance with which the tumor is supplied with capillary and larger blood vessels suggests that it may be dependent on its own vascular system for nourishment and growth, and that extensions beyond the uterus into the broad ligament lymphatics are like the branches of a tree rather than its

TABLE III. CLINICAL SUMMARY

CASE NO.	AGE (YEARS)	PARITY	SYMPTOMS	OPERATIVE TREATMENT	EXTENSION OF TUMOR BEYOND UTERUS	X-RAY THERAPY	FOLLOW-UP
1	32	III	Abdominal tumor for 6 months	Bilateral salpingo-oophorectomy; supravaginal hysterectomy	Yes	200 K.V.	Alive and well, 9 years
2	37	II	Vaginal bleeding for 4 years; hemoglobin 40%	Bilateral salpingo-oophorectomy; supravaginal hysterectomy	Yes	200 K.V.	Alive and well, 9 years
3	44	VII 13 abortions	Irregular vaginal bleeding. Abdominal tumor for 6 months. Hemoglobin 80%	Bilateral salpingo-oophorectomy; supravaginal hysterectomy	Yes	400 K.V.	Alive and well, 7 years
4	47	II	Profuse and irregular vaginal bleeding for 3 months. Hemoglobin 45%	Bilateral salpingo-oophorectomy; total hysterectomy	No	400 K.V.	Alive and well, 7 years
5	28	0	Vaginal bleeding for 2 months	*1.* Supravaginal hysterectomy; left salpingo-oophorectomy *2.* One month later, rt. salpingo-oophorectomy and removal of cervix	Yes	400 K.V.	Alive and well, 3 years
6	45	IV	Vaginal bleeding for 4 months; hemoglobin 40%	*1.* Diagnostic curettage *2.* Bilateral salpingo-oophorectomy; supravaginal hysterectomy	Yes	No	Alive and well, 6 years
7	45	0	Vaginal bleeding: *I.* Pelvic pain: Chills and fever. (Tuberculous salpingitis) *II.* Vaginal bleeding *III.* Recurrent tumor *IV.* Intestinal obstruction	*1.* Bilateral salpingo-oophorectomy *2.* Total hysterectomy, 1 year later *3.* Removal of recurrence 2½ years later *4.* Colostomy, 8 months later	Yes	No	Died, 5 years

roots. Thus, unless the extensions develop secondary vascular attachments, hysterectomy would result in a severance of their blood supply, ischemia, and death.

All of our cases and most of those in the literature were originally diagnosed as sarcoma. This diagnosis was probably made on the widespread invasion of lymphatics rather than on cytology. Goodall describes a benign and malignant type of stromal endometriosis, but this differentiation appears to rest on

the clinical course of the disease rather than on histologic criteria. Robertson included a case in his series which exhibited many characteristics of stromal myosis, but showed also cellular pleomorphism and necrosis. He designated the tumor as a malignant stromal endometriosis, but unfortunately, the case was too recent for a follow-up to have been made. Goodall's fatal cases died ten and eleven years after initial operation, while in Frank's case recurrence took place seventeen years after the removal of the primary tumor. It would appear that the lesion should be considered of low-grade malignancy with a tendency to late local recurrence.

The relationship of this tumor to endometriosis is uncertain. Goodall believes that the relationship is a close one, and considers the lesion as one type of endometriosis. Casler's case eventually developed an endometrial cyst of the ovary, and five of Goodall's cases were associated with ovarian endometriosis. These, however, were not all substantiated histologically. In our cases there were no clinical or pathologic findings suggestive of ordinary endometriosis, except in the one case which showed a small clump of three endometrial-like glands in a large subserous tumor. The growth differs from endometriosis rather markedly, however, in at least four major respects: it does not menstruate; it forms large, solid tumor masses; it extends along lymphatic and vascular channels by direct continuity of growth; it tends to recur many years after initial removal. These differences would appear to be of sufficient magnitude to warrant the recognition of the lesion as an entity distinct from endometriosis.

It is difficult to find a short descriptive name for the lesion. Frank, in 1932, suggested "endolymphatic fibromyosis," which has the disadvantage of not denoting the stromal origin of the tumor. A simple change of his descriptive name to "endolymphatic stromal myosis" retains the advantage of Frank's nomenclature, and has the added value of denoting the origin of this unusual tumor.

Summary

The clinical histories, follow-up records, and pathologic characteristics of seven cases of rare uterine tumors arising from the endometrial stroma are presented. They are similar to cases that previously have been described as adenomyoma without glands, endolymphatic fibromyosis, and stromal endometriosis. They exhibit pathologic characteristics, which in the past frequently have led to a diagnosis of endometrial sarcoma. They seem to be of low-grade clinical malignancy. Due, however, to the late recurrences which have been reported, long follow-up records are necessary before the degree of clinical malignancy of these tumors can be assessed. They occur during the years of sexual maturity and present signs and symptoms similar to those of uterine fibromyomas. Their relationship to endometriosis and adenomyosis is uncertain. Their pathologic and clinical characteristics are sufficiently distinctive, however, to warrant their separate classification. "Endolymphatic stromal myosis" is suggested as a name for these neoplasms.

I am indebted to Drs. W. G. Cosbie, C. O. White, and Roscoe R. Graham for the clinical histories and follow-up records of their private cases. I am also indebted to Dr. G. W. Lougheed, pathologist, Wellesley Hospital, Toronto, and to Dr. Lorne Whitaker, pathologist, St. Catharines General Hospital, St. Catharines, for the opportunity of studying their surgical

specimens. The high voltage x-ray treatments were given under the direction of Dr. Gordon Richards, radiologist, Toronto General Hospital, and Director of the Ontario Institute of Radiotherapy, Toronto.

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Discussion

DR. RICHARD W. TELINDE, Baltimore, Md.—Dr. Henderson has described, and again called our attention to an uncommon uterine disease, but it is a disease of which the recognition and proper handling become of the greatest importance to the individual who suffers from it. In our experience it is very rare, despite Dr. Goodall's published statement to the contrary. In our laboratory, where 65,000 specimens have been examined, we have encountered only four cases, including the first one published by Casler. Two of these were our own and two were sent in from other clinics. As further proof of the rarity of the disease, it should be noted that in most of the small series reported, including that of Dr. Henderson, the cases have been collected from more than one clinic. During these years while we have encountered these four cases, we have seen 128 cases of sarcoma of the uterus in its various forms. Of these, 79 occurred in myomas, 11 in the myometrium, 11 in the cervix, and 27 in the endometrium. So, again I cannot agree with Dr. Goodall when he states that in contrast to his views on "endometrioma interstitiale," "sarcoma of the uterus is a very rare disease." Of course, one might argue that we are confusing the two conditions, but the differentiation is quite distinct.

There are two very important points relative to this disease. Dr. Henderson has mentioned both of them:

1. Its degree of malignancy.
2. Its relation to endometriosis.

In relation to malignancy, there are two things which are quite evident.

1. Many women do not die, in spite of incomplete removal. The analogy mentioned by Dr. Henderson to the withering of the branches of a tree after cutting the trunk is quite appropriate.

2. On the other hand, some cases do recur with metastases, some of which are controlled by irradiation, and others are not. Recurrences may be very late, as in Frank's case which recurred after seventeen years. A comparable degree of malignancy is found in granulosal tumors of the ovary. Recently, we have reported three cases with recurrence and death eighteen, twenty, and twenty-one years following the removal of the primary ovarian tumor.

Most writers have assumed this disease to be a special form of endometriosis. I am pleased that Dr. Henderson has taken a guarded view of this when he states, "The relation of this tumor to endometriosis is uncertain. On histologic examination of these tumors, one is struck with the similarity of them to adenomyosis of the uterus, but to my mind there are a few important differences which should put them into a different category:

1. Cases have been reported that have recurred and progressed following complete removal of ovarian tissue.

2. More important still is the fact that some of these tumors have made their clinical appearance years after the menopause. For example, Robertson reported one in a 55-year-old woman who began to bleed three years postmenopausally Miller reported one appearing with rapid growth seven years after her last period. Our recent case caused postmenopausal bleeding at the age of 61 years, more than ten years after her menopause. I appreciate the possibility of an extraovarian source of estrogen, but the fact remains that true endometriosis does not act in a similar way after the menopause.

3. Furthermore, the percentage of malignancy is much higher in these tumors than in true endometriosis.

4. Finally, the extension of these tumors by the lymphatics is different from the mode of extension of endometriosis.

There is one point in the diagnosis of this disease which is of some practical importance. Since many of the tumors grow into the uterine cavity as well as into the myometrium, tissue may be obtained by curettage which will establish the diagnosis.

Finally, a word as to the proper terminology for this disease. As mentioned above, I believe one is not justified in assuming it to be a special form of endometriosis. I feel that the term "endolymphatic" should be omitted, because it also extends "perilymphatically" and through blood vessels. Therefore, I suggest that the disease be called "stromatosis." This term indicates that the condition arises in the endometrial stroma, the only proved etiologic fact that we have. In using this term, we must do so realizing that some forms are benign and others malignant, and that the histologic differentiation is difficult and, at this time, probably impossible.

DR. EMIL NOVAK, Baltimore, Md.—It is a well-known fact that certain types of sarcoma of the uterus, not necessarily endometriol, have a tendency to grow intravascularly and to penetrate the lymphatics. In extreme cases one can even pull out plugs of sarcoma tissue from the larger uterine vessels. I would be inclined to interpret Dr. Henderson's cases as representing low-grade sarcomas of endometrial origin. One or two of the gross pictures which he showed, especially Fig. 2, presented the massive polypoid intrauterine growth which so often characterizes endometrial sarcoma. His cases could scarcely be considered benign, since there was such extensive dissemination.

I would like to amend Dr. TeLinde's suggestion as to the terminology of these stromal growths. For the benign group, the designation of benign stromatosis has been suggested, but I believe that it is unwise to separate this type from what may be called the mother group of adenomyosis, of which they represent one variety, and a rare one at that. They are better spoken of as stromal adenomyosis. Incidentally, such a diagnosis should not be made unless numerous sections establish that the stromal tissue invading the uterine musculature is not accompanied by glands.

There is even more valid objection to the term "malignant stromatosis," also recently introduced into the literature. Stroma is a connective tissue, and the malignant connective tissue tumor is sarcoma. The malignant prototype of the so-called benign stromatosis is endometrial sarcoma, and this is what such tumors should be called. It is both unnecessary and confusing to introduce such terms as malignant stromatosis.

DR. JAMES R. MILLER, Hartford, Conn.—I recently saw a patient who presented a picture almost identical with that mentioned by Dr. Henderson. She was 38 years of age, had three children, and had lost a great deal of blood during the previous nine months, so that her hemoglobin had sunk to 40 per cent. Total excision of the uterus, tubes, and ovaries was done. Complete removal of all tumor tissue was impossible, as it extended high on each side, in fact, to the level of the kidney vessels.

One point I think is worthy of mention, and it may have some bearing on nomenclature. The silver differential stain for stroma in these tumors shows the typical basket-work pattern which is characteristic of endometrial stroma. The similarity is so striking that it leads me to believe that the derivation of these tumors from endometrial stroma should be considered when naming them.

DR. HENDERSON (closing).—Regarding the incidence of these tumors, we collected our cases over a period of nine years from three different hospitals. Four of the cases occurred at the Toronto General Hospital.

I think the discussion of Dr. TeLinde and Dr. Novak emphasized my opening remark when I said these tumors are difficult to classify as either benign or malignant. I think "stromal myosis" is preferable to the name suggested by Dr. Novak of "stromal adenomyosis," as this definitely implies the presence of glands in the tumor. Dr. TeLinde's suggested name is quite descriptive.

THE VALUE OF PLASMA PITOCINASE DETERMINATIONS IN OBSTETRICS*†

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(From the Division of Obstetrics and Gynecology, University of California Medical School)

IN THE blood of pregnant women there is an enzyme which destroys the oxytocic properties of pitocin. Until this protein is purified and characterized as to specificity and action we may refer to it simply as "pitocinase." In this study, it will be shown that the level of plasma pitocinase is a guide to both the existence and the duration of pregnancy, and that variations from the normal range point to a basic enzymatic disturbance associated with eclampsia.

Literature

The observation that pregnancy serum inactivates the posterior pituitary hormone was made by von Fekete in 1930.[1] Two years later, he showed that the oxytocic effect was reduced when the incubated mixture was tested on pregnant women, as well as when it was assayed on the isolated uterus of a guinea pig.[2] In 1935, Schockaert and Lambillon[3] demonstrated that pregnancy serum was also "antagonistic" to the vasopressor activity of postpituitary extracts, and that normal pregnant women were relatively insensitive to the blood pressure raising properties of this hormone,[4] a fact independently confirmed by Dieckmann and Michel.[5]

The enzymatic nature of this reaction was not elucidated until 1941, when Werle and his co-workers[6-8] studied the inactivating power of pregnancy blood upon both pitocin and pitressin. They demonstrated the enzyme "in the second month of pregnancy" and said that the amount "remains at a fairly constant level from the third to the eighth month, is highest at birth, and can no longer be demonstrated one month afterward." They could not detect any in the serum of nonpregnant women nor in fetal cord blood, but found traces of activity in all urine specimens and in colostrum. The optimum pH for activity was between 6.5 and 7.5. The enzyme was thermolabile and easily oxidized, but after oxidation it could be reactivated by cysteine or glutathione. No inhibiting substances could be found.

In order to understand the type of reaction with which we are dealing, we must consider our substrate. The chemistry and physiology of the posterior pituitary hormones has been reviewed recently by Irving.[9] Pitocin (oxytocin, alpha hypophamine) is a polypeptide containing at least five amino acids, has an active sulfydryl group and a molecular weight somewhere between 600 and 2,000. It is either separated or split off by chemical treatment from a large "mother" protein molecule which contains oxytocic, pressor, and antidiuretic properties in a constant proportion. When one of the peptide linkages of pitocin is split by enzymatic action, the substance loses its pharmacologic properties. Whether the oxytocic hormone of the posterior pituitary gland plays any role in the normal physiology of human reproduction has never been elucidated.

The following enzymes will *not* destroy pitocin: Crystalline trypsin,[10] carboxypeptidase[11] and pepsin;[12] concentrated preparations of bone phos-

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phatase,[12] amine oxidase, diamine oxidase (histaminase), and the fibrinolytic enzyme of activated human plasma (present study). Other enzymes, in variable concentrations, *will* destroy pitocin: Crystalline chymotrypsin and concentrates of yeast aminopolypeptidase, "angiotonase" (extracts of red blood cells or kidney),[10] tyrosinase,[13] papain, and the dipeptidases and aminopeptidases of intestine.[12] Gulland and Macrae[12] believe that the enzyme which actually destroys pitocin (i.e., "pitocinase") is not identical with any of these latter impure enzymes but is simply a contaminant.

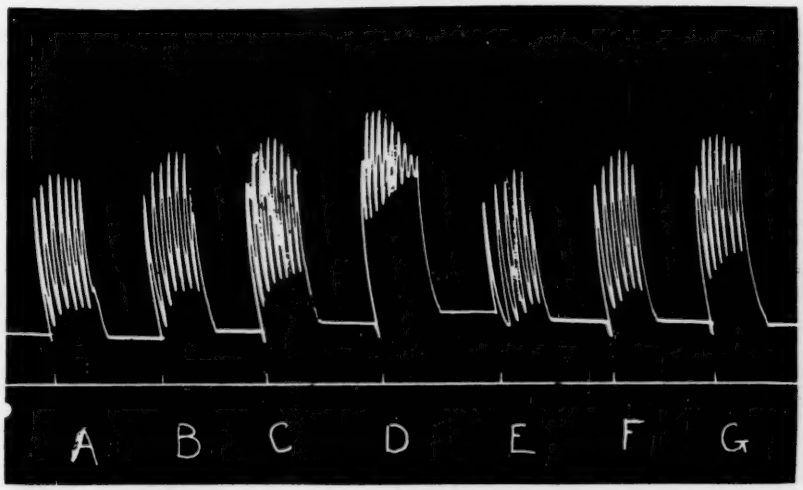

Fig. 1.—Response of isolated rat uterus to pitocin.

Tracing	Units added to 20 ml. bath	Mean rise (mm.)
E	0.01	17
A	0.025	20
B, F	0.05	22, 22
H	0.075	24
C, G	0.1	27, 28
D	0.2	37

Methods

The technique of determining the plasma concentration of pitocinase is relatively simple. Five units (0.5 ml.) of commercial pitocin are added to a known amount of oxalated pregnancy plasma, the volume is made up to 50 ml., and a few drops of toluene are added as a preservative. An initial sample of 20 ml. is withdrawn and immediately inactivated by adding one drop of 10 per cent acetic acid and placing the tube in a boiling water bath for three minutes. The filtrate represents the "zero time" or "100 per cent substrate" standard with which subsequent samples are compared. The remainder of the mixture is incubated at 37° C., and 10 ml. samples are removed at predetermined intervals and inactivated in the same manner.

The percentage of pitocin remaining in each sample is estimated by a standard oxytocic assay on an isolated uterine strip suspended in Tyrode's solution in a constant temperature (37° C.) bath of 20 ml. capacity. For this purpose, we have used the uterine horns of rats too old to breed, or rats which have been castrated two to four weeks before use.* The uteri are useful for twenty-

*Castration or advanced age reduces the spontaneous motility of the isolated uterus without materially affecting its response to pitocin. In addition to its economy, the rat uterus has the advantage of being insensitive to histamine. As an interesting and puzzling side light, we have noticed that the uteri of castrated rats respond well to pitocin only if the animals are fed lettuce or vitamin A in addition to Purina Dog Chow, or are sensitized with estrogenic hormones. We have not as yet made a systematic study of this phenomenon, but the observation suggests that there is a relationship between vitamin A and the metabolism of the estrogens.

four hours after excision if kept in Tyrode's solution in the ice box. In matching responses, the mean rise rather than the peak of the clonic response is the more accurate reflection of the dose. Some typical responses obtained are illustrated in Fig. 1. The usual precautions of bubbling oxygen next to the strip, avoiding trauma to the uterus, neutralizing and warming all solutions to be tested, and counterbalancing the tension on the uterus carefully are all essential for performing the bioassay within an accuracy of plus or minus 25 per cent.

Calculations

The destruction of pitocin by pregnancy plasma follows the kinetics of a first order reaction, and the log of the percentage remaining plotted against time gives a straight line. We have determined by repeated trials that the velocity of the reaction is independent of the amount of pitocin used and varies only with the concentration of the enzyme in the incubation mixture. Accordingly, if the time taken for half destruction is determined, the velocity can be calculated by applying the simple formula $k = \frac{0.693}{\frac{1}{2} \text{ time (minutes)}}$.[14] We have adopted 100 times k (the velocity constant) as the unit of pitocinase activity, and when this is multiplied by the dilution of plasma utilized in the incubation, the result gives the units of pitocinase per ml. of plasma. In order to estimate how much plasma to use and how long the incubation times should be, an approximate prediction of the activity must be made (from the curve of Fig. 2). The following derivation of the first formula is then useful:

$$\frac{\frac{1}{2} \text{ time (min.)}}{\text{plasma dilution}} = \frac{0.693 \times 100}{\text{estimated units/ml. plasma}}$$

A convenient incubation time is selected and the plasma diluted accordingly. Samples are removed at the estimated time for half destruction, about one-third less and one-third more than this time in order to obtain at least four points (the zero time sample being the first). Following the assay, the log of the percentage of pitocin remaining is plotted against time—most conveniently with semi-log paper—and by fitting a straight line through the four points, the time for half destruction may be easily read from the chart. Values of less than 0.1 units/ml. of plasma may be readily determined, but an activity corresponding to less than 0.05 units/ml. of plasma must be considered as doubtful.

Results

Nature and Stability of Plasma Pitocinase.—The enzyme with which we are dealing is a large protein molecule, and most of the activity may be found in that fraction salted out at one-third saturation of ammonium sulfate. Attempts at purification are difficult because the activity is so easily destroyed by oxidation. A portion, but not all, of the lost activity may be restored by treatment with cysteine. Preliminary treatment of pregnancy plasma with 0.1 molar iodoacetate does not inhibit the activity. Prolonged incubations (over six hours) are best carried out in modified Thunberg tubes *in vacuo* with a heavy layer of toluene on the surface.

Pregnancy plasma may be stored at 6° C. overnight without appreciable loss of activity, but there is a loss of 60 per cent of the activity in four days at this temperature. If the plasma is frozen, or is kept at 6-8° C. *in vacuo* or

under a heavy layer of mineral oil, there is a loss of only 35 per cent in seven days. The results to be described below were all obtained with fresh blood samples.

Distribution of Pitocinase.—Plasma samples of 20 nonpregnant subjects, including amenorrheic and postmenopausal women, showed traces of pitocinase activity between the ranges of 0.01 and 0.06 unit/ml. of plasma. These values

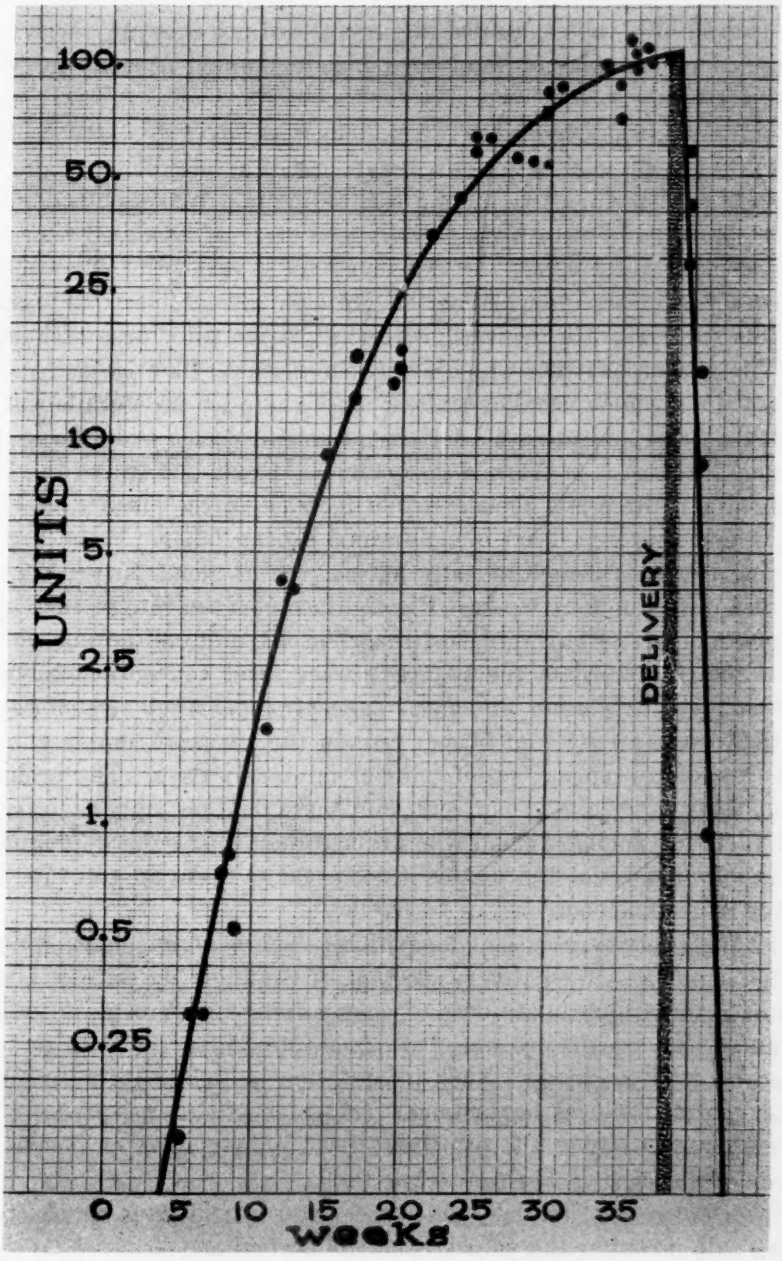

Fig. 2.—Plasma pitocinase levels in normal pregnancy.
Ordinate: Units/ml. plasma (values below 0.1 not illustrated).
Abscissa: Week of pregnancy, dating from conception.

vary with the phases of the menstrual cycle, being high at the time of ovulation and very low during menstruation. The observed activity may be due to fluctuations of a nonspecific protease rather than to the more specific peptidase under consideration. Samples from 52 pregnant women, on the other hand, were positive in 51 instances and doubtful in one. The doubtful result (less than 0.05 unit/ml.) was obtained on a woman who was but sixteen days past the date of conception as judged from her basal body temperature curve.

The plasma of a rabbit, guinea pig, or rat did not show any activity during pregnancy. Five samples of fetal cord blood obtained at delivery showed no pitocinase activity.

Packed red blood corpuscles, after hemolysis, gave the same activity per gram as full-term pregnancy plasma, regardless of species or sex. The full-term human placenta, after brief extraction with saline in a Waring blender, exhibited from 30 to 50 units of pitocinase activity per gram of tissue. It is not known, however, whether pitocin may be destroyed by a variety of intracellular proteinases and peptidases, or whether the proteins extractable from tissues which destroy this substrate are identical with the plasma pitocinase of human pregnancy. The plasma enzymes which destroy angiotonin likewise increase in pregnancy, but to a much smaller extent, and there is no parallelism between "angiotonase" and "pitocinase" activity either in plasma or in tissue extracts.[15]

Plasma Pitocinase in Normal Pregnancy.—From the 4th to the 38th week after conception, there is a thousand fold increase in the plasma pitocinase concentration, and this high level is maintained during labor. Following delivery, the enzyme decreases logarithmically at the rate of about 25 per cent per day until it disappears in four weeks. Fig. 2 illustrates the rate of increase during normal pregnancy. (Four values of less than 0.1 unit/ml. do not show on this chart.) From the third to the sixteenth week after conception, there is a *100 per cent increase in plasma pitocinase concentration every twelve days.* Even though there were an error of 50 per cent in the bio-assay, one might therefore date the time of conception within plus or minus six days. The probable error of our bio-assay is within 25 per cent, and there does not appear to be much individual variation among women who are less than four months pregnant. During the last four months, the scatter is too great to make an accurate prediction of the date of confinement.

Following abortion, the same logarithmic decline of pitocinase concentration occurs that is noted after delivery; so that, if we know the date of abortion, we can calculate the approximate date of conception. Conversely, if we know how far advanced the pregnancy was, we can approximate the date on which the completed abortion occurred. Such information is limited in its usefulness, but might assume medicolegal importance. Of prognostic value, perhaps, would be the knowledge of whether the pitocinase level is increasing or decreasing after an episode of bleeding in the first trimester

Twins (two cases), triplets (one case), and intrauterine death of the fetus (two cases) do not alter the values from the normal range.

Plasma Pitocinase in Pre-eclampsia and Eclampsia.—When true pre-eclampsia or eclampsia supervenes, an interesting phenomenon occurs (Fig. 3).

Of the 16 cases studied to date, only three had plasma pitocinase levels which fell within the normal range. Seven had values which were high, and six had values which were low for the corresponding period of pregnancy. There is no apparent correlation between the severity of the disease and the plasma pitocinase level. In the seven cases of eclampsia, for example, three values were high, one was normal, and three were very low. In two cases of pregnancy complicated by severe arteriolar hypertension, normal values were observed.

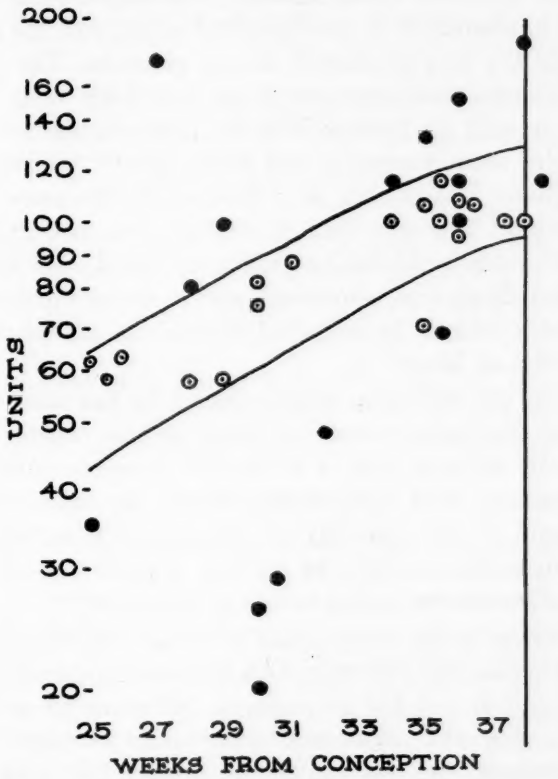

Fig. 3.—Plasma pitocinase levels in pre-eclampsia and eclampsia (solid circles), compared with the normal range for the last trimester (open circles).

Discussion

It is interesting to compare these observations on pitocinase with the exhaustive studies which Ahlmark recently made on the histaminase activity of pregnancy plasma.[16] This latter enzyme, which is a diamine oxidase having no inactivating properties upon pitocin, nevertheless has a similar thousand fold increase during pregnancy. In contrast to pitocinase, the histaminolytic enzyme appears somewhat later and levels off sooner, but it demonstrates the same logarithmic increase during early pregnancy. Ahlmark claims that from the fifth to the fourteenth week after conception he can estimate the duration of pregnancy within six days. The method for plasma histaminase determination is somewhat more cumbersome than that for pitocinase, but it is already being used in Stockholm as a routine pregnancy test and as a prognostic aid in cases of threatened abortion.[17] In pre-eclampsia and eclampsia, plasma his-

taminase values are likewise scattered on both sides of the normal range, and again there is no apparent correlation between the value and the severity of the disease.* The present observations, together with those of Ahlmark on histaminase[16] and Smith and Smith on serum fibrinolysin,[18] suggest that there is a basic enzymatic disturbance associated with eclampsia.

The source of plasma pitocinase in human pregnancy is not known, but the most reasonable hypothesis is that the trophoblastic syncytial cells contribute this protein to the maternal blood stream. The enzyme can be detected about three weeks after implantation of the fertilized ovum, and the rate of increase in the blood parallels the rate of growth of the placenta. The increase continues long after the histologic disappearance of the Langhans' cells. The protein is of sufficient size to prevent its passage into the fetal circulation. We have mixed the plasma samples from pregnant and nonpregnant women, and have found that the nonpregnant plasma acts as a diluent, in the same manner as saline solution. This would indicate that pitocinase does not exist normally as a zymogen which is simply activated by pregnancy blood. We know nothing about the physiologic significance of pitocinase, and it seems rather strange, speaking teleologically, that a woman is protected maximally against a natural oxytocic hormone at the onset of labor.

If both pitocin and pitressin are destroyed by the same enzyme, and even though all of the destruction were to occur in the plasma, as suggested for angiotonin,[19] it can be seen that a pitocinase concentration of 100 units/ml. in a normal pregnancy near term would permit the inactivation within forty-five seconds of half of any quantity of postpituitary hormone injected intravenously. This may account for the relative insensitivity of normal pregnant women to the blood pressure raising action of pitressin.[4, 5]

Since the uterine horns of an elderly female rat may be used for many tests at a negligible cost, the determination of plasma pitocinase may prove to be a rapid and economical test for pregnancy. Whether its accuracy approaches that of a urinary chorionic hormone determination remains for further study. With careful technique, the test has the additional advantage during the first four months of determining the week of pregnancy, and during the last four months it may be of value in the differential diagnosis of pre-eclampsia from other hypertensive disorders. At the present time, we are searching for some substrate other than pitocin, so that chemical or colorimetric titration may replace the more inaccurate and somewhat tedious bioassay.

Summary

Very early in pregnancy, an enzyme capable of inactivating pitocin appears in the blood, and a method for its quantitative determination is described. The properties, kinetics, stability, and distribution of pitocinase are discussed.

During the first four months of human pregnancy, the plasma concentration of this protein increases logarithmically in such a fashion that not only the

*As a tentative explanation, the essential change in pre-eclampsia may be an elevated level of both pitocinase and histaminase. In half or more of the cases, large protein molecules may be lost through the glomeruli, thus clearing the plasma of the enzymes at a rate exceeding their accumulation. This is based on the finding of low plasma and high urinary values for pitocinase in one case of eclampsia.

existence, but the week of pregnancy may be closely approximated. In true pre-eclampsia or eclampsia, the plasma levels are scattered on both sides of the normal range, indicating that an enzymatic disturbance is associated with this disease.

Appreciation is expressed for the able assistance of Mrs. Dean Rucker and Miss Eleanor Enos.

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Discussion

DR. CARL BACHMAN, Philadelphia, Pa.—Dr. Page's careful quantitative study of the inactivation of posterior pituitary extracts by pregnancy plasma draws attention to a little-known sector of the field of enzyme physiology. I should therefore like to comment on a few of the theoretical, rather than the practical implications of his work.

His demonstration of the strikingly consistent and remarkable rise in concentration of "pitocinase" during pregnancy arrests attention as being a new contribution to our knowledge, and well worth further investigation. It would be interesting, for example, to know more about the nature and specificity of this enzyme. Dr. Page has indicated that it may be active against substances other than pitocin, and this, if true, would enhance its physiologic and clinical interest. Indeed, I think he is doing rather less than justice to his own good work by his coinage and use of a term having so narrow a meaning as "pitocinase."

It would also be interesting to know more about the site of formation or release of this enzyme during pregnancy. Dr. Page has suggested its probable production by the growing trophoblast, and this would seem to be its most likely source. However, one should bear in mind that a similar, and conceivably identical, enzyme is richly distributed intracellularly in several tissues, including the erythrocytes of men and nonpregnant, as well as pregnant, women. It is, therefore, at least theoretically possible for such a pre-formed intracellular enzyme to be released during pregnancy through altered conditions of cell permeability. In this connection the possible role of the sex steroids suggests itself, for it will be remembered that these steroids appear in plasma during pregnancy in a rising curve of concentration very strikingly comparable to that which Dr. Page has demonstrated for "pitocinase." Of course, the apparent absence of the enzyme in fetal plasma argues against the possibility suggested, unless it can be shown that the preformed enzyme is also absent in fetal tissues and erythrocytes. But the notion would bear examination, if only to enable us to have a firmer theoretical floor under the proposed use of this enzyme reaction as a specific diagnostic test of pregnancy. As "leads" it might be useful to test for the presence of the enzyme in such conditions as hemolytic ictero-anemia and obstructive jaundice. Another interesting

test would be the examination of those species of animals in which the estrogen "spiegel" of the plasma during pregnancy resembles that of the human—for example, the mare.

These are admittedly only a few, and rather unimportant, suggestions prompted by Dr. Page's stimulating report. All must agree that he has done a workmanlike job of investigation and has made a real contribution. Its future development will be followed with great interest.

DR. CHARLES H. PECKHAM, JR., Hartford, Conn.—The theoretical aspects of Dr. Page's paper have been discussed by Dr. Bachman. I should like to make a few remarks concerning practical applications of this work which may develop in the future. First, it seems likely that the method may become somewhat commonly employed in diagnosing pregnancy. Most of the tests in use up to the present time carry with them a sufficient percentage of error as to leave a good deal to be desired. In Dr. Page's series there was one doubtful reaction, while the others were clearly positive or negative. Furthermore, the test is not a time-consuming one and, frequently in obstetrics, problems arise where time is the essence of diagnosis.

Before reading the paper, I hoped that it might produce something to add to our knowledge of the cause of the onset of labor. It is a matter of general agreement that the uterus in early pregnancy reacts very little to pitocin. The reaction increases as the pregnancy advances, and is greatest at about the time of the onset of labor. It is puzzling to find an enzyme in the plasma capable of inactivating pitocin, and particularly to find it in highest concentration at a time when the uterus is most sensitive to an oxytocic substance.

It is, furthermore, difficult to understand why an enzyme apparently elaborated by the placenta should take four weeks after the extrusion of this organ before it has entirely disappeared. Also, if we assume that the enzyme is a product of the placenta, why would not the concentration decrease as soon as the product of conception dies? Finally, placentas delivered after the estimated date of confinement frequently show evidences of senescence. One would suspect in these cases a decrease in plasma pitocinase, but such was not Dr. Page's findings.

The problem as to why the plasma pitocinase level was high in certain cases of toxemias and low in others deserves further investigation, particularly since there was no clinical differences found in the two groups. I believe the essayist should conduct follow-up studies on these patients in order to ascertain whether some of them developed permanent vascular damages while others did not.

DR. PAGE (Closing).—So far as the occurrence of pitocinase in closely related species are concerned, I have had no opportunities to obtain such material, but a pregnant monkey would be a welcome addition to my group of patients.

I failed to mention that when this method is used as a qualitative test for early pregnancies, the fresh plasma and pitocinase incubated *in vacuo* in a Thunberg tube, with a heavy layer of toluene on the surface, for eighteen hours. Of 20 additional tests on women who were less than eight weeks pregnant, all have been positive, while only traces (less than 0.05 units/ml. of plasma) have been found in nonpregnant subjects. We have not found a subject who suspected pregnancy in less than seventeen days after conception.

CYCLIC CHANGES IN THE PHYSICAL AND CHEMICAL PROPERTIES OF CERVICAL MUCUS*

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THE escape of a vaginal discharge, which rustic herdsmen have long regarded as a sign of estrus in their stock, finds its counterpart at midcycle in the human female. This discharge, which intelligent and observant women[1] and clinicians recognize as a second flux in the menstrual cycle, is traceable to the cervix.[2] While one may infer that this mucus normally contains increments from the uterus, it is not yet known to what extent the endometrium contributes to the character of the mucus which collects at the external os.

Rhythmic changes in the cervical glands with greatest development in the second half of the cycle have been described by Hartman[3] in the monkey, and by Wollner[4] in women. Sjövall,[5] however, noted that the proliferation reached its highest point at the time of ovulation, and thus gave a histologic explanation for the secretory changes, which can be observed directly by clinical examination. It is at the time of ovulation during the phase of maximal follicular development that the greatest yield of clear mucus may be obtained at the cervical os.[6] This finding has also been observed following supracervical hysterectomy. Since women upon whom bilateral oophorectomies and supracervical hysterectomies have been performed may be stimulated to the production of large amounts of clear mucus by the administration of estrogens, it seems established that the cervical glands are susceptible to or controlled by hormones.[2]

One may here join in with the speculations of others concerning certain functions of cervical mucus. On a priori grounds, one might attribute to it a protective function shared by the secretions of other mucous surfaces. By its replenishment, it may well aid in the removal of foreign bodies, cellular debris, and bacteria enmeshed in its substance. DeLee[7] regarded the mucus as presenting a barrier to the uterus against infection, a view again expressed by Goodall in 1945.[8] However, the evidence as to how the mucus exercises this property, apart from its action as a physical obstruction, has to my knowledge not been adducted.

The current interest in antibiotics stimulated an investigation now in progress by a colleague, Dr. Charles Carpenter. The data now on hand suggest that cervical mucus, in vitro, may inhibit the growth of certain strains of *Streptococcus hemolyticus* and *Staphylococcus aureus,* and enhance the growth of certain strains of *Neisseria gonorrhoeae* (Table I). This latter finding, i.e., the apparent encouragement to the growth of *N. gonorrhoeae,* given

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

TABLE I. EFFECT OF CERVICAL MUCUS OF NORMAL WOMEN ON BACTERIA

ORGANISM	METHOD OF TESTING*	RESULTS†
Streptococcus hemolyticus	Plates streaked	50% showed inhibition
	Plates poured	63% showed inhibition
Staphylococcus aureus	Plates streaked	67% showed inhibition
	Plates poured	80% showed inhibition
Neisseria gonorrhoeae	Plates streaked	72% showed enhancement

*Cervical mucus, in amounts ranging from 6.7 to 226 mg., was introduced into suspensions of 24-hour cultures of the organisms indicated. After two hours of incubation at 37° C., plates were poured or streaked.

†The colonies were counted after twenty-four hours' incubation and compared with counts made on the control cultures containing no cervical mucus. None of the resultant cultures of Streptococcus or Staphylococcus in media containing cervical mucus showed enhancement, and none of like cultures of *Neisseria gonorrhoeae* showed inhibition.

by the addition of cervical mucus to the culture medium, may add significance to the observed persistence for many months of gonorrheal infections in cervices which remain otherwise fallow.

From their observations on cattle, Woodman and Hammond[9] regarded the liquefaction of mucus, such as occurs at estrus, as a requisite to the free progression of spermatozoa through the cervix. A gradient in electric potential of 3 to 5 millivolts between the zone of contact of cervical mucus (pH 9 to 9.6) and semen (pH 7 to 8) has been described by Miller and Kurzrok.[10] They suggest that this difference in potential may be a directing factor in the first orientation of spermatozoa in the female genital tract. Using in vitro methods, these same workers observed that when the mucus is infected, highly viscid, and opaque, the sperm in the proximity to it will not congregate at its boundary, nor will they try to penetrate the mass.

Séguy, in 1933,[11, 12] qualitatively described an increased amount of cervical mucus at the time of ovulation as determined by direct inspection of the ovaries. At this time the mucus was noted to be most translucent, acellular, and penetrable by spermatozoa. Similar qualitative results were reported by Lamar,[13] who introduced an improved technique for studying the penetration of cervical mucus by spermatozoa. Inasmuch as spermatozoa are ejaculated into an entirely new environment, and since their initial task is to overcome the obstacle of cervical mucus, the characteristics of this secretion at different times of the menstrual cycle appeared to be of sufficient importance to justify a quantitative in vitro study of factors which might assist or hinder the migration of spermatozoa through the cervical canal.

Experimental

Subjects.—Young women, for the most part medical students or laboratory technicians, who were in good health, and who had normal menstrual cycles and normal pelvic findings, served as subjects in these studies. Basal temperature records of all these subjects showed a typical midcycle shift from a lower to a higher level. This, with collateral evidence, has been regarded as a sign of ovulation.

Collection of Material.—Cervical mucus was obtained throughout the cycle, save during menstruation, by aspiration from the external os and from the cervical canal. An effort was made to obtain all the mucus available at any one time. All specimens were weighed.

Results

Amount of Mucus.—Although the production of mucus varies from cycle to cycle and from subject to subject, the monthly patterns are quite similar.

When the amounts of mucus obtained are plotted on a scattergraph, one notes that the maximal production occurs on about the fourteenth day of the usual 28-day cycle. A fairly abrupt rise in the amount of mucus is noted before the fourteenth day, and a sharp fall afterwards. At the time of the peak production, a ten- to twelvefold increase is noted over the 20 to 60 mg. quantity present in the postmenstrual and premenstrual periods.

In these studies, it was observed that a time relationship exists between mucus production and the basal temperature shift.[6] The maximal secretion is noted to occur in the two-day period during which the rise in the basal temperature takes place. Gross tests also indicated that the viscosity of the mucus is lowest at this time of greatest output, a phenomenon described qualitatively by Séguy[11, 12] and Lamar.[13]

Viscosity.—Cervical mucus as it collects at the external os is not homogeneous and does not behave as a true fluid. Such complex properties as density, surface tension, tackiness, film formation, and dispersibility influence its fluidity. Possible admixture with endometrial secretions and contact with the vaginal acidity and flora may well alter its flow characteristics. However, by using an objective method for measuring the fluidity,[14] one finds that the resistance to flow of mucus through a capillary tube, expressed as viscosity, decreases as one approaches the midcycle. The lowest viscosity, though variable over a period of a very few days, occurs at the time of ovulation coincident with the shift of the basal temperature. At this time the output of mucus is greatest. Mucus which requires as much as 100 seconds to traverse a given distance through a capillary tube, a condition typical of the postmenstrual and premenstrual periods, is replaced at midcycle by a thin watery secretion having such fluidity that only 2 to 3 seconds are required for it to negotiate the same distance under the same set of standard experimental conditions.

Penetrability of Mucus by Spermatozoa.—When the fluidity of mucus, expressed as the converse of the viscosity, and the penetrability of mucus by spermatozoa are graphically compared, a high degree of correlation is noted.[14] At midcycle, when the mucus possesses its lowest viscosity, spermatozoa may travel through it at the rate of 3 mm. or more per minute. Before and after the ovulatory phase, their progress through the mucus may be reduced to less than 0.25 mm. per minute; in fact, at times the attempts of the spermatozoa to negotiate the mucus barrier fail entirely.

Water Content.—The fluidity of mucus at midcycle suggested that its water content is greatest at this time. By test it was determined that the water content of cervical mucus ranges from 92 to 94 per cent in the postovulatory and preovulatory phases. This low figure may be due to the high cellular content. At midcycle, as indicated by the thermal sign of ovulation, the water content rises to 97 to 98 per cent. This fact might of itself help to explain the increased penetrability of mucus by spermatozoa at this time (Fig. 1).

The copious outpouring of mucus at midcycle, in contradistinction to the menstrual flow, appears to involve but little cell destruction and loss, since the secretion at this time is translucent and relatively acellular. It has not been possible to do actual cell counts because of the difficulty of effecting satisfactory dispersal of the mucus with its enmeshed cells over a grille. During the phase of low output the mucus is viscid, opalescent, or even turbid. These turbid or opalescent specimens, on microscopic examination, are found to be very rich in cells and debris.

Chemical Content.—MacLeod[15, 16] made the significant observation that the metabolism of human spermatozoa suspended in Ringer-glucose solution is largely glycolytic, and that aerobic glycolysis amounts to about 80 per cent

of the anaerobic. Substrates containing such utilizable sugars as glucose, maltose, mannose, fructose, and glycogen were found to be essential for the maintenance of glycolysis and prolonged activity of the spermatozoa.

Since sugar is such an important factor in the metabolism of human spermatozoa, it is but natural that it should be supplied by the ejaculate. Huggins and Johnson[17] demonstrated that the glucose content of semen, which averages about 300 mg. per cent,[17, 19, 20] is derived from the seminal vesicles. MacLeod[18] has shown that 75 per cent of the spermatozoa are present in the first 40 per cent of the normal ejaculate. McCarthy[19] has shown that incubation for twenty-four hours reduces the glucose content of semen to 10 to 25 per cent of the original level.

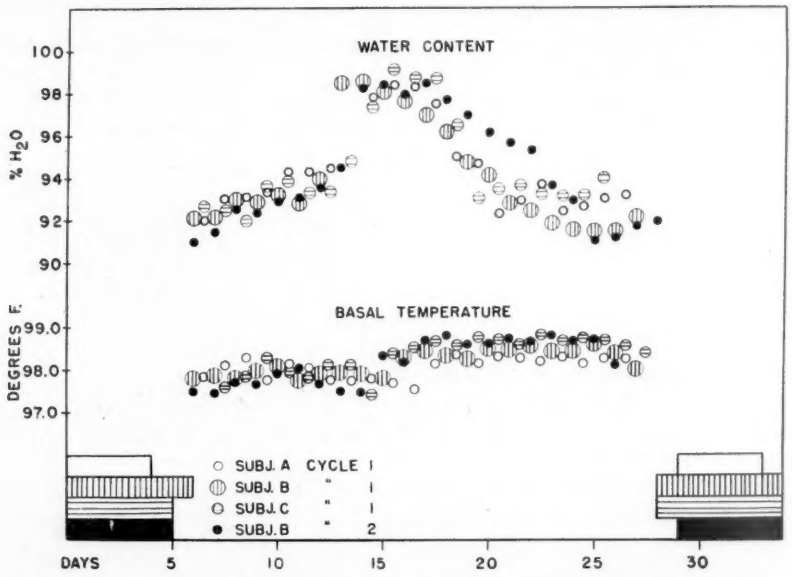

Fig. 1.—The Increase in water content of cervical mucus at the time of ovulation as indicated by the shift in basal temperature. Three subjects; four cycles.

Hughes[21] and Novak[22] have recently called attention to the important part played by glycogen in the nutrition of the egg before and after fertilization, and also after nidation. As though to anticipate this requirement, the genital tract is generously supplied with this carbohydrate. Since the sperm cells on penetrating cervical mucus carry with them no substantial reservoir of sugar, MacLeod[23] has hypothecated that in all probability they find a suitable substrate in the female genital tract to maintain their motility. This suggestion led to an investigation in our laboratory of the carbohydrates in cervical mucus.

The cycle, exclusive of the menstrual period, has been divided arbitrarily into three phases: preovulatory, ovulatory, and postovulatory, the ovulatory period corresponding to those days during midcycle on which the amount of mucus is markedly increased. The daily results have been averaged according to the phase of the cycle (Table II). The Somogyi modification[24] of the Shaffer-Hartman copper reagent has been used for the determination of the amount of reducing substance present.

When mucus is added to the copper reagent, it is found to contain a small amount of free reducing substance. Whether this reducing substance is actually a carbohydrate is not yet known.

If a weak iodine solution is added directly to the mucus, mahogany colored mottling and streaks are seen, a reaction indicating the presence of

TABLE II. CONCENTRATION OF REDUCING SUBSTANCES IN CERVICAL MUCUS

	PREOVULATORY PHASE (% GLUCOSE)		OVULATORY PHASE (% GLUCOSE)		POSTOVULATORY PHASE (% GLUCOSE)	
Free Reducing Substances (4 cycles)						
Draining	0.11		0.05		0.12	
Canal	0.09		0.04		0.16	
Glycogen Precipitation Method						
1. Free reducing substance in precipitate						
Draining	0.02		0.01		0.03	
Canal	0.00		0.00		0.00	
2. Free reducing substance in supernatant						
Draining	0.08		0.06		0.15	
Canal	0.08		0.03		---	
3. Acid hydrolysis of precipitate (6 cycles)						
Draining	0.32		0.23		0.27	
Canal	0.15		0.05		0.20	
4. Acid hydrolysis of precipitate and supernatant of same mucus specimen	ppt.	super.	ppt.	super.	ppt.	super.
Draining	0.38	0.24	0.19	0.20	0.60	0.16
Canal	0.19	0.28	0.10	0.14	0.14	0.14
Direct Hydrolysis (5 cycles)						
Draining	0.55		0.41		0.79	
Canal	0.60		0.31		0.83	

glycogen. When the mucus is dissolved in strong alkali followed by the addition of 95 per cent alcohol, a standard procedure for the determination of glycogen, a precipitate is thrown down which also gives the characteristic color reaction with iodine. This precipitate contains little, if any, free reducing substance, but after acid hydrolysis measureable quantities of reducing substances can be determined. If the precipitate is glycogen, glucose should be formed on hydrolysis; preliminary fermentation studies show that approximately 60 per cent of this hydrolytic product is fermentable. The supernatant obtained from the treatment of cervical mucus with strong alkali followed by the addition of alcohol contains amounts of free reducing substance comparable to those found in untreated mucus, and acid hydrolysis of this supernatant solution yields even larger quantities of copper reducing substances.

Acid hydrolysis of the mucus itself yields larger amounts of reducing substances than by any of the methods previously mentioned. Direct hydrolysis would, of course, measure all the reducing substance that mucus might contain. From the data at hand, there appears to be a cyclic variation in the amount of fermentable sugars following direct hydrolysis. In the preovulatory phase, 48.7 per cent of the glucose concentration was fermentable, 28.7 per cent in the ovulatory phase, and 49.8 per cent in the postovulatory phase.

In all of the carbohydrate studies a cyclic variation in the concentration of the reducing substance is noted, with the lowest concentration occurring during the ovulatory phase. This fact would appear to be correlated with the acellularity characteristic of this period of the cycle.

Since the amount of reducing substance obtained by direct hydrolysis is greater than the sum of that obtained from the untreated mucus plus that obtained by hydrolysis of the glycogen precipitate, the presence in the mucus of reducing substances other than carbohydrate was sought. Hewitt[25] found that tyrosine had approximately the same reducing power as dextrose, and

TABLE III. COLOR REACTIONS GIVEN BY CERVICAL MUCUS

NAME OF TEST	REACTION PRESUMABLY DUE TO PRESENCE OF
1. Iodine test	Glycogen
2. Biuret reaction	Peptide linkage
3. Millon's reaction	Hydroxy-phenyl group, as in tyrosine
4. Liebermann's reaction	Condensation of tryptophane with an aldehyde or other carbonyl group
5. Xanthoproteic reaction	Phenyl group, as in phenylalanine, tryptophane, and tyrosine
6. Sulfur test	Unoxidized sulfur, as in cystine

NOTE: These reactions were obtained on both draining and canal specimens. The color reactions given by mucus obtained during the ovulatory phase were usually fainter than those given by samples obtained during the pre- and postovulatory phases.

tryptophane about 80 per cent as much. In his work he used the Hagedorn-Jensen reagent, which is slightly more sensitive than copper reagents to reduction by noncarbohydrate compounds. In the belief that certain amino acids may account for some of the reduction of the copper reagent, tests for their presence were made on the mucus. Color reactions were obtained that are characteristic of the peptide linkage; the hydroxy-phenyl group, as in tyrosine; the condensation of tryptophane with an aldehyde or other carbonyl group; the phenyl group, as in phenylalanine, tryptophane, and tyrosine; and unoxidized sulfur, as in cystine (Table III). The color reactions were usually fainter in the ovulatory phase than in the preovulatory and postovulatory phases. This fact is probably due to the acellularity and high water content of the mucus at this time.

The presence of amino acids in cervical mucus is strongly suggested by these color reactions. What their significance may be is not established. One may here offer the presumption that they share with carbohydrate the function of nutrition of the gametes, and perhaps also of the fertilized egg.

Summary

Cervical mucus at midcycle is increased in amount, acellularity, water content, and fluidity. Furthermore, cervical mucus at this time is well supplied with carbohydrate and presumably amino acids. From a teleologic standpoint, we may conclude that because of these characteristics the sperm, on deposition in the vagina, find an environment propitious for their nutrition and migration through the cervical canal.

The author wishes to acknowledge the very able assistance and cooperation of his associate, Dr. Ellenmae Viergiver, in the prosecution of this study. This investigation has been aided by a grant from the Ortho Research Foundation.

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Discussion

DR. JOHN ROCK, Brookline, Mass.—Dr. Pommerenke and his colleagues are developing for us factual standards and actual measurements. The uterus is a highly differentiated organ, good for only one thing, reproduction. The egg gets in at one end and, in spite of the fact that Pincus has already been able to start rabbit eggs on their way to growth by the use of only heat or salt, spermatozoa must enter the other end to fertilize the human egg. In order to reach it, they must have a proper medium, and Dr. Pommerenke has limited his discussion to the fluid in one small segment of the uterus.

I approve of the term "ovulatory phase." We hear much about the variation in the amount and the quality of mucus through the menstrual cycle. There is a short period at first when it is scanty. Then comes the ovulatory phase, at some time in which ovulation takes place, and during which mucus is plentiful. Tests for ovulation indicate, I believe, an ovulatory phase, and not necessarily the moment of ovulation.

The fluid in the cervix, as has been said, may be very profuse. Frequently patients complain of leucorrhea, which is not necessarily pathologic, but merely the result of hyperfunction of normal glands. The condition is usually limited to about a week and does not necessarily require treatment. However, sometimes this discharge is so profuse as to merit attention. Nevertheless, it would be a great mistake so thoroughly to treat the cervix by diathermy as to relieve the patient's complaint, and yet leave the cervix so dry that spermatozoa could not make progress through it.

Dr. Pommerenke's report of Dr. Carpenter's demonstration of the bactericidal property of cervical mucus at ovulation time is very interesting. Perhaps it explains how uncommon it is for the millions of sperm to infect the susceptible tube through which they travel after leaving semen that is often highly contaminated. But the gonococcus does get into the tube. Do the sperm carry it through the mucus which in vitro favors its growth?

Dr. Pommerenke has pointed out various qualities of this mucus which possibly serve the purposes of sperm. Such investigative work is bound to be of great practical value in the control of conception, having in mind, of course, the positive rather than the negative aspects of this high function.

The time factors are interesting. The egg is probably susceptible to fertilization for only a matter of perhaps twelve to forty-eight hours after its release from the follicle. Spermatozoa are functional for probably forty-eight hours. It takes the good ones only three to four hours to travel from the vagina to the ampulla of the tube. Where do they get the energy to do this? MacLeod has shown that sperm in vitro live longer and are progressively motile longer if their medium contains some easily utilizable sugar. But during the ovulatory phase, Dr. Pommerenke finds that the concentration of reducing substances like glucose is less than at other times. The fluid of the ejaculate is high in carbohydrate, but sperm are in this for only a short time. Nor can there be much for them in the uterine fluid, since glycogen does not appear in appreciable amounts in the

endometrial glands until after ovulation. Perhaps, though they can use carbohydrate, good ones do not need much, if any. Three times pregnancy has been established in hitherto barren women after injecting into the uterus a twice-washed suspension of husband's spermatozoa in Ringers-Locke's solution that contains only 0.1 per cent of dextrose. It is conceivable and worthy of contemplation that the varying carbohydrate content of the cervical and uterine fluid, together with other chemical constituents and physical qualities, may have more direct reference to phylogeny than to physiology. They may be inherited factors passed down from long distant ancestors, in whom they were physiologically useful, to much differentiated humans in whom they persist but have no function. Whether or not this is so can only be determined by studies similar to those of Dr. Pommerenke.

DR. ISIDOR C. RUBIN, New York, N. Y.—The secretion of cervical mucus under normal and pathologic conditions, its physical and chemical composition and properties, and its specific purposes are matters which have been dealt with in a more or less desultory manner in the past. This has not been due to lack of interest so much as to the difficulties involved in the technical study of cervical mucus. One of the chief reasons for active revival of interest in this subject has been the importance of bringing relief to childless married couples who increasingly enlist sympathetic medical advice to enable them to have children. Dr. Pommerenke's paper is therefore welcome as a serious attempt to solve theoretical questions concerning cervical mucus.

That there are cyclic changes in the cervical secretion may be accepted both on the basis of the new evidence presented by Dr. Pommerenke and numerous clinical and histologic observations. A hormonal relationship between ovarian function and the secretion of cervical mucus has been held for a long time; and cervical erosion has also been suspected of being the result of dysfunction of the ovaries.

We have struggled with this question for some years at Mount Sinai Hospital and had planned to attack the problem somewhat along the same lines as those of Dr. Franklin Hollander of the Department of Physiology, who has done much work on gastric and intestinal mucus. But with the intervention of the war which brought on difficulties in getting needed apparatus, together with the shortage of man power, we had to abandon the full program.

Evidently Dr. Pommerenke was able to solve the matter of getting the specimens of mucus in sufficient quantities upon which to make determinations. We aspirated the cervical canal under varying degrees of pressure up to 20 pounds in some cases, and in others we applied cellulose or aluminum caps to the cervix for several hours. In normal cases we were not able by aspiration to get enough mucus for the tests we had planned. The pathologic cases gave us more mucus but, after aspirating it into a pipette with an expanded collecting chamber, it was difficult to remove the specimen for testing. This was later solved by devising a sort of trap-door collecting chamber with removable parts. In obtaining the pH of the cervical mucus in situ, difficulties were encountered because we had no suitable electrode and could not have one constructed.

Concerning the behavior of spermatozoa in cervical mucus, a few observations with the Hühner test and artificial insemination may be mentioned. There have been instances where spermatozoa remained motile after one or two hours in the vaginal secretion, although the spermatozoa found in the cervical secretion were nonmotile. The cervical mucus under such circumstances was not necessarily viscid or grossly altered. In most cases it was scanty. As a rule, motility was observed in the cervical mucus, while the sperm in the vaginal secretion were nonmotile. In some cases spermatozoa have been found to remain actively motile in thick muco-pus for a longer time than in the vaginal secretion.

The predominant number of oval or olive-shape heads of the spermatozoa in the cervical secretions in contrast to the spear or pear-shape heads of the spermatozoa found in the vaginal secretions and in the fresh unmixed ejaculate is a phenomenon not yet explained. Does the sperm head change on account of some physico-chemical property of cervical mucus which causes it to swell, or does the cervical mucus select these sperma-

tozoa out of the millions that make their way into the cervical canal, i.e., are there particular gametes present in the ejaculate in a certain percentage which find their way into the cervical canal? When semen containing spermatozoa with predominantly spear-shaped heads was mixed with cervical mucus, practically all the heads assumed the olive shape. This observation was made many years ago and subsequent observations have corroborated it.

The question of what constitutes endocervicitis clinically is another pertinent point of interest. Endocervicitis characterized by profuse mucopurulent discharge from the cervix and a high content of pus cells may be cleared up by the newer sulfonamide chemotherapy which, at the same time, demonstrates its infective nature. But there are many variations in the amount of cervical mucus and in the numbers of pus cells which may be found at all times of the menstruation-ovulation cycle. Are these findings analogous to those in the vaginal smear during the menstruation-ovulation cycle or shall we designate them as mild or moderate endocervicitis? Should it be found on the basis of a larger number of cases that mucus secretion is more abundant, containing no pus cells, and that it is less viscid on the fourteenth day of the menstrual cycle, it may be advanced as additional indirect evidence of ovulation, although it may prove eventually not to have such specific significance. Dr. Pommerenke apparently takes it for granted that the cyclical diphasic change in temperature is pathognomonic.

I think a point which should be borne in mind in connection with this discussion is that there is a marked difference between normal fertile couples and sterile matings. In sterility, resort to coitus during the so-called favorable period has been highly disappointing. There are undoubtedly other physical and chemical properties of the cervical mucus besides mucin and fluidity which favor, or militate against, penetrability and motility of spermatozoa. Whether they are immunologic in nature remains for the future to disclose.

Such investigation is especially tedious and requires the devotional cooperation of the young women submitting to the frequent examinations. Only the keenest interest and enterprise in prosecuting this particular work can yield data such as Dr. Pommerenke has been able to present. There is great need for more work of this kind. I should like to ask him in closing to describe some of the essentials of the technique for the guidance of others who may be similarly interested.

DR. POMMERENKE (Closing).—When the cervical secretion is scant it is almost always highly cellular. This can be demonstrated by microscopic examination when a great deal of cellular debris can be demonstrated.

As regards technique, the dry speculum is inserted into the vagina exposing the cervix. The mucus adhering to the surface is wiped away to prevent contamination of the specimens which are removed with a pipette attached to a suction syringe. One may ask how you get the mucus out of the pipette? This may be quite a job. Clean pipettes containing the secretion are emptied into test tubes and rinsings added. At times only about 20 mg. of secretion can be obtained. A high percentage of this is water. Microchemical methods are available for studying even such minute quantities of material.

GRAPHIC PORTRAYAL OF RELATIVE PELVIC SIZE*

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TWO general classifications of the bony pelvis exist, the etiologic and morphologic. The first, based upon manual mensuration, defines limits of normality of inlet size according to Litzmann, and of the outlet according to Williams, but disregards the midpelvis. The latter, developed by Caldwell and Moloy, is based upon the roentgenologic determination of pelvic shape and its effect upon the course of labor, but offers no criteria of size. Both classifications are complicated, and neither is of practical value to the medical student, general practitioner, or average obstetric specialist. There is need for a simple method of evaluation of pelvic adequacy. The purpose of this paper is to offer a visual method of depicting three essential pelvic planes in contrast with established norms. Results obtained from application of this method will be presented in a forthcoming communication.

The obvious method of evaluating size and shape of any passageway is to measure the length and breadth of each of a sufficient number of cross sections. Graphic reproduction of each cross section, especially when plotted on a sheet of paper in comparison with established norms, offers a clear and a visual conception of variations of contour. Since the total height of the bony pelvic cavity measures approximately 5 cm anteriorly and 10 cm. posteriorly, it is obvious that graphic portrayal of but three cross sections will provide sufficient knowledge of contour. Moreover, since bony dystocia of serious nature occurs most often at the inlet, less commonly at the midplane, and rarely at the outlet, these three pelvic levels were chosen for graphic portrayal. The contour of each plane can be sketched with reasonable faithfulness from knowledge of its anteroposterior and transverse diameters, and the point where they intersect. Admittedly, this method does not permit reproduction of the *exact* outline of each plane, and may not satisfy serious students of pelvic morphology, but the resulting diagram is sufficiently true to permit accurate prognostication of the course of labor.

In order to diagram each of the three pelvic levels, a normal gynecoid pelvis was selected and the outline of each level accurately obtained by shaping lead wire to its anatomic contours. The resulting shapes were corrected for minor variations and adjusted to accepted pelvic measurements. Ideal shape and size of the inlet, mid-, and outlet planes of an average, normal pelvis on a life-size scale were, therefore, accurately reproduced on paper. In addition, a centimeter scale was incorporated directly in the anteroposterior and trans-

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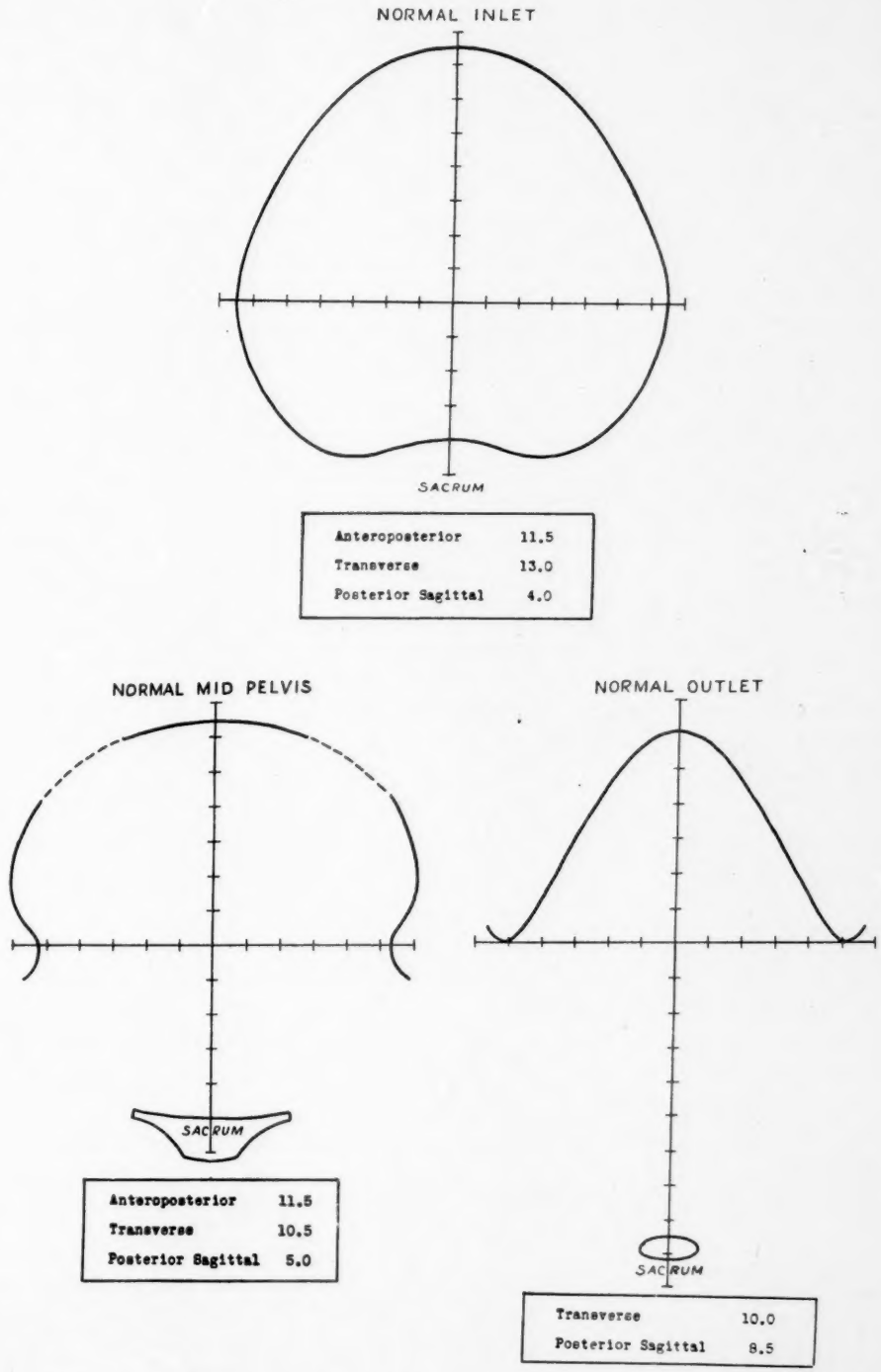
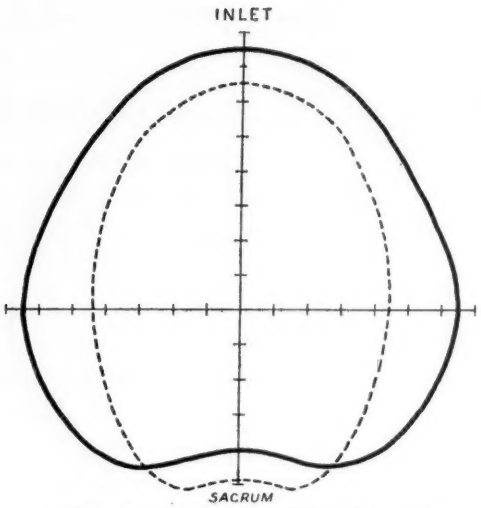
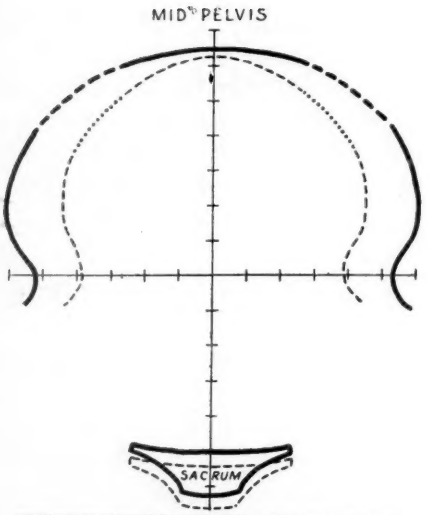


Fig. 1.—*A*-inlet, *B*-mid, and *C*-outlet planes of a normal gynecoid pelvis. The diagrams were obtained by shaping lead wire to the anatomic contours of the pelvis, correcting for minor variations, and adjusting to accepted pelvic measurements. The scale is in centimeters.

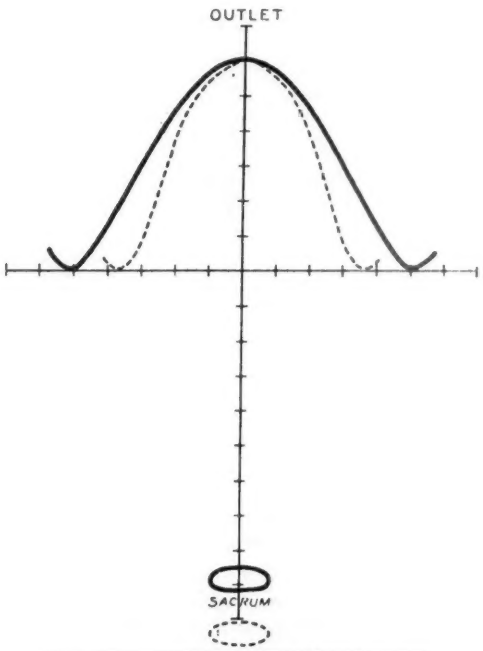
NOTE: *All* illustrations are reduced to the same size for the sake of ready comparison.



	Normal	Patient
Anteroposterior	11.5	11.4
Transverse	13.0	8.8
Posterior Sagittal	4.0	4.9



	Normal	Patient
Anteroposterior	11.5	11.7
Transverse	10.5	7.7
Posterior Sagittal	5.0	5.4



	Normal	Patient
Transverse	10.0	7.3
Posterior Sagittal	8.5	10.1

Fig. 2.—The dotted lines represent graphically an anthropoid type of pelvis of patient M. J. She was delivered by elective cesarean section because it was felt the head would not pass the midplane.

verse diameters. In practice, the outline of each plane is sketched on the basic diagram of its normal counterpart. Obviously, it is necessary to know where the two diameters intersect. The transverse diameter is exactly bisected by the anteroposterior unless there is unilateral pelvic distortion. On the other hand, the point at which the transverse diameter crosses the anteroposterior of each of the three planes is variable and must be determined by measurement of the posterior sagittal diameter. This can be accomplished for the inlet and midplane only by roentgenographic means. The technique of manual measurement of the posterior sagittal of the outlet is familiar to every obstetrician.

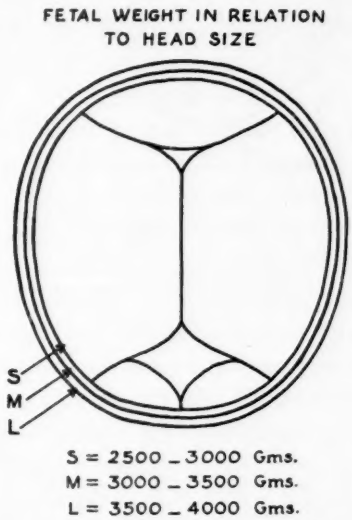


Fig. 3.—Fetal head diagram. In practice, this is made of a 2-mm. thick piece of transparent plastic, shaped to the contour of the largest size. The other two outlines are etched into the plastic.

Inlet contour (Fig. 1-*A*) is familiar from frequent portrayal, but the midplane is seldom illustrated (Fig. 1-*B*). Cross section diagrams of the outlet cannot be made, since there are two triangles in different planes, but with a common base. For the sake of completeness, however, both triangles may be projected as a plane (Fig. 1-*C*). The graphic depiction of a distorted pelvis in immediate contrast with the normal is so vivid that an assistant resident obstetrician said, "Now we are able to *see* the patient's pelvis!" The vividness of mental impression is examplified by the following patient (Figs. 2-*A*, *B*, and *C*). This is a typical anthropoid pelvis and it seemed obvious that vaginal birth of a living, term-sized child would be difficult or impossible, especially with regard to the midplane. An elective cesarean section resulted in the birth of a 2,528 Gm. living child.

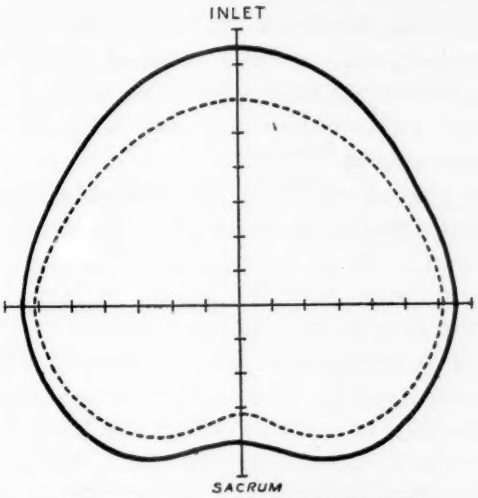
Decision concerning management of any given patient is greatly facilitated by applying a diagrammatic, transparent, plastic cutout of small, average, and large fetal heads to the graphic, pelvic diagrams (Fig. 3). From available tables, cephalic outlines corresponding respectively to infants weighing between 2,500 and 3,000 Gm., 3,000 and 3,500 Gm. and 3,500 and 4,000 Gm. were constructed. Due allowances were made for the normally flexed position of the fetal head during the process of birth. The inclusion of all three sizes on a

single piece of transparent plastic further simplies the apparatus. Predetermination of fetal size is difficult and inaccurate, even with present roentgenologic methods of fetal cephalometry. Nevertheless, this plastic, cephalic cutout has proved its practical value. Generally speaking, when a given sized cephalic outline can be fitted exactly into the pelvic diagram, it may be concluded from a clinical standpoint that a child of equivalent size plus 500 Gm. can pass through the patient's pelvis. The 500 Gm. excess is probably accounted for by the process of molding.

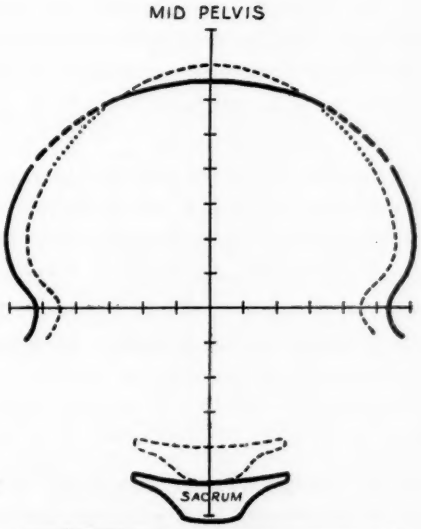
With graphic portrayal of pelvic size and approximate shape in direct contrast with the normal, and by use of plastic cephalic cut-outs, it has been possible to make accurate prognostications of the course of labor. For example: A 29-year-old primigravida, at term, hospital number W-27796, was admitted Aug. 19, 1945, in labor, but with a floating head. Graphic representation of the pelvis revealed generalized contraction of inlet and midplane (Figs. 4-*A*, *B* and *C*). The child was estimated to be average in size. It was predicted the head would engage transversely, arrest at midpelvis, and that forceps rotation to obliquely anterior with extraction would be necessary, since the head could not traverse the midplane either in occipitoanterior or occipitotransverse position. This is precisely what happened. After a total labor of 32 and one-fourth hours, with a second stage of three and three-fourth hours, the head was arrested in left occipitotransverse position just above the ischial spines. Kjelland forceps were applied. The operator could not rotate at the level of arrest, and could not produce descent without rotation. By combination of both, he was able to bring the head through the mid-pelvis obliquely anterior, with subsequent easy extraction. The child weighed 3,692 Gm., and was gaining weight at the time of discharge.

Recapitulating, knowledge of six pelvic diameters will give all practical information necessary for evaluation of pelvic capacity. These diameters are the anteroposterior and transverse of the inlet and midplane, and the posterior sagittal and transverse of the outlet. Four of the six measurements can be obtained or closely estimated manually: the anteroposterior of the inlet; the transverse and posterior sagittal of the outlet; and the transverse of the midplane. Two pelvic measurements, the transverse of the inlet and the anteroposterior of the midplane, are measured in the living by roentgenographic means. From a practical standpoint, the transverse diameter of the midplane is commonly measured roentgenographically, although in 1930 Hanson described an instrument for its manual mensuration.

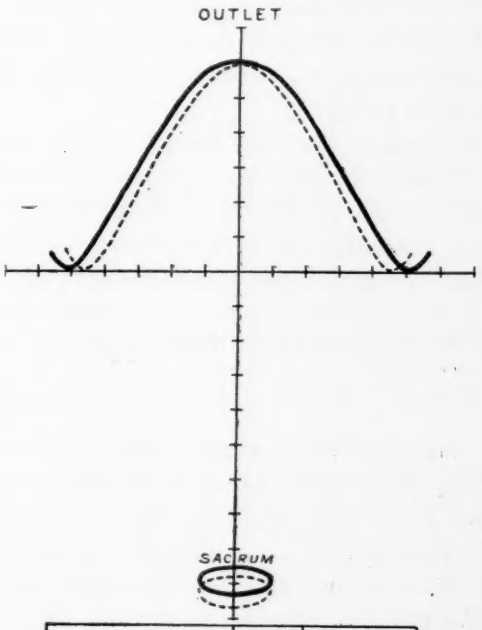
Ordinary roentgenograms are worthless in the evaluation of pelvic size, because the rays emanating from the tube target are not parallel and, therefore, enlarge the image. The enlargement is inconstant and depends upon the distance of the x-ray film from the object and from the target. Some form of correction is essential to determine size. Any acceptable roentgenologic technique will supply the measurements needed for graphic portrayal of pelvic planes. However, the methods generally employed are technically difficult and complex. Snow introduced a much simplified method of roentgenographic mensuration in 1940, based on geometric principles and employing a specially devised slide rule. In both conception and practice, it is within the capabil-



	Normal	Patient
Anteroposterior	11.5	9.2
Transverse	13.0	12.3
Posterior Sagittal	4.0	3.2



	Normal	Patient
Anteroposterior	11.5	11.0
Transverse	10.5	9.0
Posterior Sagittal	5.0	4.0



	Normal	Patient
Transverse	10.0	9.1
Posterior Sagittal	8.5	8.8

Fig. 4.—The dotted lines represent graphically the pelvis of patient E. M. It was predicted that engagement would occur in the transverse diameter of the inlet, that arrest would occur just above the midplane, and that the head would have to be drawn obliquely through the midplane with forceps. Furthermore, completion of rotation to a direct occipitoanterior below this level would be followed by easy extraction. This is precisely what happened. The second stage of labor lasted three hours and forty-five minutes.

ities of any physician willing to spend the few hours necessary to learn the basic principles and techniques. After a minimal amount of practice, any pelvic diameter may be measured within limits of error of a few millimeters. Moreover, only two films, an anteroposterior and a lateral, and the very simplest of calculations are involved.

It is no part of the purpose of this paper to discuss roentgenologic pelvimetry, except to emphasize that it is necessary for determination of two of the essential measurements. It is doubtful if graphic portrayal of relative pelvic size is necessary in patients with average, or larger, manual measurements, since associated midplane contraction is unlikely. On the other hand, as manual measurements approach the lower limits of normal according to Litzmann and Williams, midpelvic contraction becomes increasingly probable, and the need for accurate study of the *entire* bony pelvis increases. When roentgenographc evaluation is necessary, it is obviously desirable to make all measurements from the films rather than to depend in part upon manual methods.

Standards of inlet and outlet contraction sufficient to modify the course of labor are well recognized and do not need to be repeated here. Standards of midplane contraction are not well established, but are rapidly being formulated as experience accumulates. This is quite understandable when we remember that outlet contraction was defined by Williams so recently as 1909, and that midplane contraction could be recognized readily only after the advent of roentgenographic mensuration. Midplane contraction has not received sufficient attention, although it is becoming increasingly apparent that it is a definite entity.

Ideally, it would be desirable to determine the six basic pelvic diameters necessary for graphic representation on all obstetric patients. It is becoming the practice at Parkland Hospital to measure them in all primigravidas, and each multigravida with a history of difficult labor. With ever-present financial restrictions, this is not always possible, and it is, therefore, desirable to establish indications for roentgenographic mensuration of the midpelvis. This will be the subject of a forthcoming paper.

Summary

A method of graphic portrayal of size and approximate shape of inlet, mid-, and outlet planes is presented. This is accomplished by diagramming each plane on a graphic outline of its normal counterpart. Six measurements, the anteroposterior and transverse of the inlet and midplane, and their point of intersection, and the posterior sagittal and transverse of the outlet are sufficient for graphic portrayal. Four of the six measurements can be obtained, or closely estimated, manually. Roentgenographic mensuration is necessary for the transverse diameter of the inlet, the anteroposterior of the midplane, and the determination of the point of intersection of the two basic diameters of each of these levels. It is desirable for determination of the transverse diameter of the midplane. When roentgenographic mensuration is performed, it is obviously better to make all measurements from the films than to depend in part upon manual mensuration.

By means of graphic portrayal of relative pelvic size, accurate prognosis is possible. It is also possible to make precise prognosis of modifications of the course of labor occasioned by mild cephalopelvic disproportion.

References

1. Hanson, Samuel: Am. J. Obst. & Gynec. 19: 124, 1930.
2. Snow, W., and Lewis, F.: Am. J. Roentgenol. 43: 132, 1940.
3. Williams, J. Whitridge: Surg., Gynec. & Obst. 8: 619, 1909.

Discussion

DR. HENRY C. HESSELTINE, Chicago, Ill.—Drs. Mengert and Eller are entitled to forthright commendation on this presentation, for their contribution offers an ingenious method for evaluation and visualization of pelvic planes. The apparent ease and precision of mensuration invite further study. By using the same methods and units of measure, scientific comparisons are possible. As Dr. Mengert indicated, the one purpose of this paper was to present a method for depiction of the pelvic planes, especially the midplane.

We at the Chicago Lying-in Hospital have not had an opportunity to try this method yet. We employ routinely the basic measurements of the conjugate diagonals and bisischial diameters and general palpation for pelvic alteration. This last reference includes degree of prominence of ischial spines, changes in the sacrum and other parts of the bony pelvis. Whenever measurements under the normal limitation or variations are encountered, special and individual attention is given to the patient. At this time, we may use the Caldwell and Moloy classification, as an additional prognostic aid.

Internal pelvic measurements give us only the maximum space available. These concrete measurements do not offer any information about the soft tissues of the pelvis. These efforts to determine pelvic size in no way shed light upon the quality of labor which may be expected. Although the essential pelvic diameters may be accurately determined, it is not possible to be as exact on fetal size and mensuration.

We teach that the sequence of labor and delivery by the vaginal route takes place not by the rule of simple formula, but because there are multiple favorable factors. These factors as we all know them are: the available and usable pelvic capacity, the physiologic elastic pelvic soft tissues, good quality and quantity of uterine contractions with normal uterine mechanisms, and, finally, a passenger that can conform to these conditions without alteration or by physiologic molding.

As we become more adept in discovering or predicting the deviations from normal, the more we may safeguard the welfare of the mother and her baby. For this reason alone, this contribution of Mengert and Eller is valuable.

I urge Dr. Mengert to continue with his proposed program, to give it a clinical trial, and to explore the various uses and limitations. Until then, caution must be presented lest those inexperienced with these tools and unacquainted with their use employ this procedure incorrectly or, possibly, dangerously.

Thoms and Schumacher (Am. J. Obst. & Gynec. 48: 52, 1944) in their article "The Clinical Significance of the Midplane Pelvic Contraction," said, . . . "We wish to emphasize that although the knowledge of essentially exact pelvic measurements should never replace sound clinical judgment, which obviously includes the evaluation of the size of the child, character of the labor, etc., the intelligent consideration of such knowledge should form an important aspect of scientific obstetrics."

DR. KARL M. WILSON, Rochester, N. Y.—This method that Dr. Mengert presents impresses me as one of value and a very ingenious one which should be extraordinarily helpful. However, radiographic methods, after all, really offer the only satisfactory—in fact, the only possible means of obtaining accurate measurements of the midplane, corresponding rather closely to what used to be called the plane of least pelvic dimensions. The importance of this region as a site of dystocia is considerable, of course, and all of us, I am sure, have had the experience of arrest of the head in this region and a delivery completed by a difficult midforceps operation. What we want, of course, is an accurate method of radiographic cephalometry, but of that we have no hope.

(Slide.) This is a person who had some inlet contraction, slight midplane contraction, neither very well marked but very definite, and the outlet was normal. We felt that it was quite possible for her to go ahead with her labor and so we allowed that to continue. The head has already a certain degree of moulding, but even before that phase we thought it would be all right.

The lateral view shows the posterior sagittal about 1 cm. shorter than the average normal. In this case the head became arrested at the level of the spines, necessitating a very difficult midforceps operation. Fortunately, the baby was all right and the mother suffered only a moderate degree of soft parts injury. Of course, if one gets accurate measurements, we can recognize a marked degree of contraction, and those patients should be delivered by abdominal operation rather than by dragging the baby through with midforceps.

One of the things that radiographic methods particularly bring out is the shape of the pelvis. The old manual techniques gave us some idea about measurements, but told us nothing of the shape of the pelvis.

This picture is rather startling at first, and if one had only that to go on one would say that this woman could not possibly have a spontaneous delivery. Yet she did have a normal spontaneous birth.

(Slide.) This is another rather startling one discovered on x-ray, an old fracture. They are increasingly common in these days of automobile accidents. The question was: could this patient have a spontaneous delivery, and should we let her go into labor? She had a quick, two-hour labor.

I believe that this radiographic method presented should prove of considerable value. Dr. Mengert's opinion evidently differs somewhat from that of Dr. Thoms in that we can have a normal outlet and normal inlet more often than we realize, and yet have isolated midplane contraction.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I am a little dubious about the interpretation of this method of pelvic study. Dr. Mengert rather deprecates radiologic measurements because of the distortion of structures. Yet, the two most important measurements he uses are obtained by radiologic methods. I would judge that this might at once throw an error into the study. Judging from his enthusiasm, I expect he has found some way of overcoming the possible error. One could be somewhat dubious, however, when the two most important measurements are somewhat uncertain.

DR. MENGERT (Closing).—I was taught that contraction of a degree to cause dystocia occurred most often at the inlet, seldom at the outlet, and almost never at the midpelvis. Since then it has become obvious that midpelvic contraction occurs more often than outlet, and probably more often than inlet contraction.

The bony pelvis is not very tall, since its total height is 5 cm. anteriorly and 10 cm. posteriorly. If one knows the contour of three cross sectional planes, he will have all necessary information regarding the bony pelvis. If the top and bottom cross-sections are of sufficient size, average or better, there is little chance of serious midplane dystocia. On the other hand, if the top and bottom cross-sections are at the lower limit of normal, there is good chance of midplane contraction; a sort of hourglass type of pelvis. My interest in this began many years ago with just this type of patient with inlet and outlet measurements within the normal range, but at the lower limit of normality. She had a midplane contraction necessitating a difficult midforceps extraction, with a resulting dead baby.

Since each of the three essential planes can be depicted graphically from knowledge of two diameters, it is necessary to ascertain these measurements. Three of them can be obtained very well manually. The other three are not so readily measured, and one of them, the transverse of the inlet, is impossible to measure manually. Therefore, in actual practice we depend on the x-ray for measurement of the transverse of the inlet and for the transverse and anteroposterior diameters of the midplane.

Any of the various and current x-ray techniques will give satisfactory measurements within a few millimeters.

THE TIME FOR POSTPARTUM STERILIZATION*

Report of 150 Cases
Bacteriologic Studies on the Postpartum Uterus

FRANK E. WHITACRE, M.D., MEMPHIS, TENN.

WITH THE ASSISTANCE OF

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(From the Departments of Obstetrics and Gynecology of The Peiping Union Medical College, Peking, China, and The University of Tennessee College of Medicine)

IN 1936, I suggested early postpartum sterilization. Adair and Brown,[1] in 1939, kindly acknowledged the suggestion, extended the time for operation to within the first twenty-four hours after delivery and reported 50 cases. They were well satisfied with their results. In 1940, Hewitt and Whitley,[2] using the same technique, reported a study of 100 patients sterilized by this method one hour following delivery and were also enthusiastic in support of the procedure. Although we have frequently employed the Pomeroy technique and found it to be satisfactory, only the Madlener type of tubal sterilization is included in this report. It is not intended that the relative merits of the Madlener, Pomeroy, and other methods of sterilization be discussed, but rather the time for postpartum sterilization.

That occasions arise in obstetric practice when prevention of pregnancies is imperative to the future welfare of a mother and her family is commonly accepted. Such situations are usually associated with those toxemias of pregnancy, the damage from which is augmented by future pregnancies, as well as with tuberculosis, cardiac, renal and mental diseases, and other conditions. Multiparity may be the predominant issue, or a combination of circumstances may combine to form an indication for sterilization.

History

In 1919, and twice thereafter, Madlener[3-5] described the method of sterilization which bears his name. The technique is almost entirely based upon the work of Friedemann[6] who, in 1906, reported one case in which he crushed an area in both Fallopian tubes by means of the Mikulicz clamp, but recommended the Doyen clamp (later used by Madlener) and ligated the crushed area with catgut. He did not mention ligating a knuckle of the tube, nor did he use nonabsorbable suture material for the ligature, but otherwise the method was the same as that described by Madlener. There have been several modifications of this technique and some controversy as to its reliability, but the method as detailed by Madlener has given encouraging results.

Method

If an analgesic has been used during labor, many patients are still feeling the effects soon after delivery. However, to insure the patients' comfort 0.01 Gm. of morphine sulfate may be given by hypodermic injection or 0.2 Gm. of sodium

*Read (by invitation) at the Sixty-Ninth Annual Meeting of the American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

amytal by mouth, one hour before operation. In all cases the abdomen is prepared and draped for operation and a local anesthetic of 0.5 per cent procaine hydrochloride may be used. At present we are using continuous caudal analgesia in selected cases and occasionally continuous spinal anesthesia if labor is progressing unusually rapidly. We have found these methods to be especially applicable to early postpartum sterilization. Immediately after delivery the

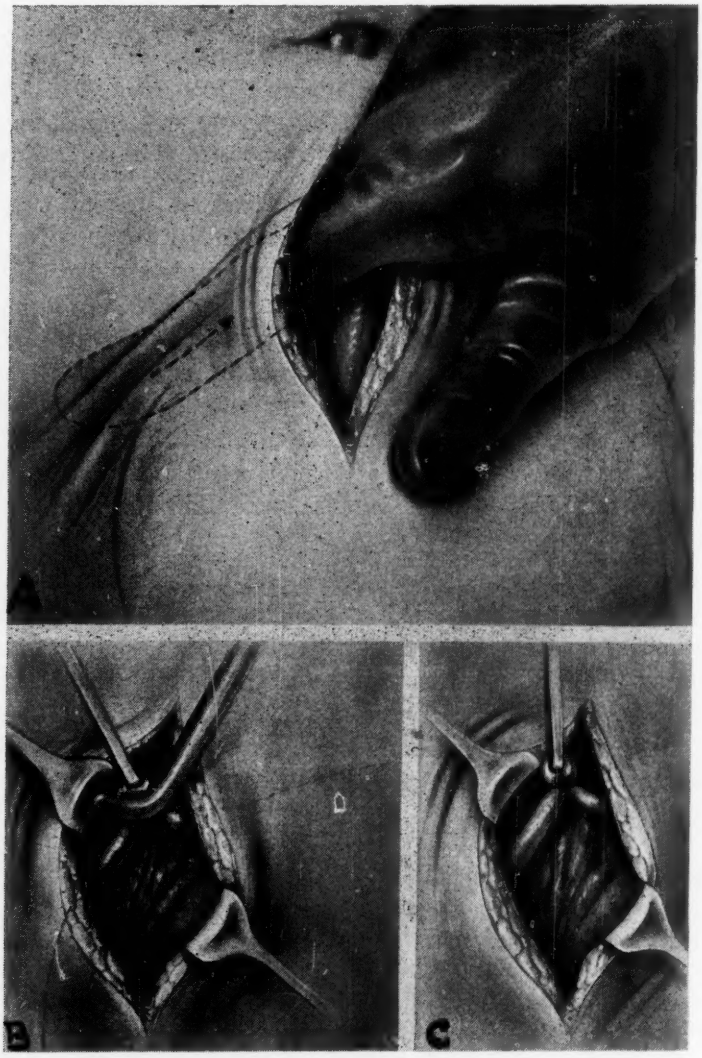

Fig. 1.—*A.* The index finger is inserted into the abdominal cavity and over the round ligament through a subumbilical incision one and one-half inches long. The uterus is rotated to bring the fallopian tube into the incision.

B. The fallopian tube is elevated with an Allis forceps and crushed with a heavy clamp.

C. The clamp is replaced by a ligature of heavy silk.

uterus is an abdominal organ rather than pelvic and, therefore, more easily approachable than after involution has taken place. The fundus of the newly delivered and contracted uterus is readily palpable, and at this level in the midline below the umbilicus, an incision one and one-half inches in length is made through the skin, subcutaneous fat, fascia, and peritoneum. This affords sufficient space to insert the index finger over the round ligament (Fig. 1-*A*). The

uterus is moved or rotated on its longitudinal axis to bring the corresponding Fallopian tube into the incision, where it is seized with an Allis or Babcock clamp and lifted upward. The knuckled tube, including a small portion of the mesosalpinx, is clamped across with a crushing instrument. This must be carefully done to paper thinness and without breaking the serosa, as recommended by Madlener.[3] At first we used a crushing intestinal clamp for this purpose, but, finding it inconvenient to use in a small area, substituted a heavy clamp with a short powerful jaw 9 mm. wide, provided with longitudinal serrations (Fig. 1-*B*). The Fallopian tube is thus doubly crushed, leaving the clamp in place for one-half minute, and ligated with double heavy black silk (Fig. 1-*C*). The procedure is repeated on the opposite tube, and the small abdominal incision closed in layers. It is more important to proceed carefully, especially in crushing and ligating the tube, than it is to hurry, but the operation should not take longer than fifteen to twenty minutes. Some authors have suggested placing a third ligature on the tube. This seems unnecessary and could be harmful. The crushed and ligated area which is proximal to the uterus is the important one, and, if the serosa is injured, resulting in a tuboperitoneal fistula at this point, a failure results regardless of other ligatures.

Material

We present a résumé of 50 postpartum sterilizations performed in the Department of Obstetrics and Gynecology of the Peiping Union Medical College during the years 1939 and 1940, by the technique just described and a series of 100 cases from the Department of Obstetrics and Gynecology of the University of Tennessee College of Medicine from 1939 to 1946. There is nothing in common between the Chinese and American series other than that the time and technique of operation are the same, and the indications are similar. We do not intend to go into the details of individual cases. The indications in general for both groups were as shown in Table I. Henceforth in this discussion the series of cases from Peking will be mentioned as Group 1, and the series from Memphis as Group 2.

We did not operate upon any patient with actual or potential infection as far as we could judge. Multiparity was included as an indication for sterilization, inasmuch as most of these were indigent patients who live under poor

TABLE I. INDICATIONS FOR POSTPARTUM STERILIZATION

	GROUP 1	GROUP 2
Multiparity	23	33
Multiparity with pre-eclampsia	5	5
Multiparity with eclampsia	0	2
Multiparity with anemia	3	9
Hypertensive cardiovascular disease	2	12
Essential hypertension	0	4
Varicosities	0	4
Pulmonary tuberculosis	6	4
Renal disease	0	16
Hydronephrosis	0	1
Nephrosclerosis	0	1
Lymphopathia venereum	0	1
Hyperthyroidism	0	1
Myocardial insufficiency	0	1
Rheumatic heart disease	10	0
Bronchial asthma	0	2
Polycythemia vera	0	1
Diabetes mellitus	1	1
Mental deficiency	0	1
Psychosis	0	1
	50	100

social and economic conditions. All of Group 1 had given birth to five or more babies—some to as many as twelve, and the average parity was 5.6, while in Group 2 the average parity was 6.7, and some had given birth to as many as fifteen babies. We considered that such a woman had done her duty, and that the children in the family were entitled to the future protection of the mother. Anemia, unless severe, was not included as an indication, for a considerable proportion of all our indigent patients are anemic as judged by the usual standards.

TABLE II. GENERAL INFORMATION

	GROUP 1	GROUP 2
Age and Parity		
Average parity	5.6	6.7
Average age	33 yrs.	28.2 yrs.
Mortality, Morbidity, and Stay in Hospital		
Mortality	0	0
Morbidity	12.5%	6%
Average stay in hospital	13 days	9 days
Length of Labor		
Shortest labor		1 hr.
Longest labor		46 hrs.
Average labor	10 hrs.	12 hrs.
Time Elapsing Between Delivery and Operation		
Shortest interval	1½ hrs.	1 hr.
Longest interval	8 hrs.	18 hrs.
Average interval	2½ hrs.	3⅛ hrs.
Type of Delivery		
Breech assisted	1	5
Low forceps	2	3
Spontaneous	47	92
	50	100

Forty-seven patients in Group 1 delivered spontaneously, two were delivered by low forceps, and one by breech extraction. In Group 2, 92 were spontaneous deliveries, and eight were assisted. The average age in Group 1 was thirty-three years, and average duration of labor ten hours; while in Group 2 the average age was twenty-eight years, and the average length of labor was twelve hours. The average stay in the hospital was thirteen days in Group 1 as compared with an average postpartum hospitalization of nine days for patients in Group 2. This compares closely with the average obstetric hospitalization without intervention of this nature. These operations in each series were done by approximately twelve members of our house staff under the supervision of the resident physician. There was no mortality, thrombosis, or embolism in either group, and, according to the standard approved by the American Committee on Maternal Welfare, the morbidity was 12.5 per cent for Group 1 and 6 per cent for Group 2. The standard mentioned is that any patient with a temperature of 38° C. (100.4° F.) or more on any two days after the first twenty-four hours postpartum, oral temperature readings being made at least four times daily, is febrile. There was one postoperative complication in each series, and that was wound infection which prolonged hospitalization to about three weeks.

Time for Operation

The time when this operation should be done in the postpartum period is the crux of the situation, and the technique used in this report is that of Madlener. By early postpartum sterilization, it is not meant to disturb the patient by surgical intervention the instant her baby is born, but rather to carry out the procedure as soon after delivery in well selected cases as is consistent with good

judgment, and with due regard to the local and general condition of the patient. Following infection as manifest by the presence of fever, the most frequent and serious complication of the immediate postpartum period is hemorrhage. In recognition of this fact, the rules of hospitals require, or should require, that the patient remain in the delivery room undisturbed for one hour after delivery, or until the period of bleeding is over. In the absence of bleeding at the end of one to two hours after delivery, one may assume that there is little danger of hemorrhage. Skajaa[7] sterilized 126 patients by the Madlener technique from the second to the twenty-ninth days postpartum. There were seven cases of thrombosis and one of embolism in the group operated upon after the fourth day. The uterus and other pelvic organs were disturbed at the height of involution and at a time when the uterus contains pathogenic bacteria, as has been shown by studies on the bacteriologic condition of the puerperal uterus. Skajaa also reported one case of thrombosis occurring in a patient sterilized on the second day. In a study of the bacteriologic condition of the puerperal uterus, by means of intrauterine cultures taken on an average of 3.2 days after delivery, Douglas and Rhees[8] found anaerobic and aerobic streptococci in 73.6 per cent of all patients studied. Loeser[9] found bacteria in the upper cervix in 25 per cent of his cases on the first day post partum. Kulka[10] believes that bacteria invade the uterus even during labor. Adair[1] and again Diamond[11] came to the sound conclusion that postpartum sterilization should not be done after the first twenty-four hours. Thornton and Williams[12] reported a group of 309 sterilizations, 178 of which were combined with appendectomy. There was a morbidity of 21 per cent, one fatality, thromboses, and other complications in those operated upon after the first day, and the highest morbidity was in those done on the eighth day. Still they conclude that there is no relation between the time of operation and the postoperative complications. It is not our policy to combine postpartum sterilization with any other elective procedure. Knight[13] has reported a series of postpartum sterilizations with a morbidity of 19.7 per cent. The only patients reported as having fever were those who were operated upon from the third to the sixth days postpartum. Still the author concludes that the fourth or fifth postpartum day is the safest time for performing this operation. It is probable that bacteria find their way into the uterus much sooner after delivery than is commonly appreciated. It is our opinion that postpartum sterilization can be done by this method with a considerable degree of safety in well selected cases within the first few hours after delivery, but in view of the dangers of hemorrhage and infection, the patient is best protected by carrying out the procedure from one to two hours after delivery. The average time elapsing between delivery and sterilization was one and one-half hours for Group 1 and three hours for Group 2. Not included in this report were three cases who were operated upon on the third, fourth, and sixth postoperative days, contrary to the policy of the department. Two of these cases were morbid.

Reliability of the Madlener Operation

Failures have been reported in regard to this type of operation on the tubes as in most operations for sterilization. Rubovits and Kobak[14] found endosalpingiosis in one case, and Adair[15] found tuboperitoneal fistula in two cases as causes of failure. Dippel[16] has reported five failures, four of which were due to avoidable causes, whereas the fifth, due to endosalpingiosis, was probably unavoidable. On the other hand, this type of tubal operation has had considerable success. In 1932, Madlener[3] reported that 86 patients previously reported had had no pregnancies in a period of nine years, and a review of reports in the literature totaling 4,279 patients sterilized by Madlener's technique, v. Graff[17] found that the operation was successful in 99.6 per cent of the cases. We have been handicapped in an attempt to follow these patients because the war made

it impossible to follow up Group 1, and there has been insufficient time to follow Group 2, but we know that one patient from Group 1 and two from Group 2 became pregnant after sterilization.

Advantages

The advantages of early postpartum sterilization are evident. It is simple, safe, and relatively bloodless. Methods of contraception are often unreliable. Patients in whom sterilization is imperative and who are instructed to return to their physician months after delivery for this purpose, seldom do so unless pregnant. An operation to sterilize even ten to fifteen days after delivery must be considerably more extensive, thereby increasing the risk. The necessity of doing a cesarean section for the purpose of sterilization, although probably frequently done, is hereby eliminated. Future hospitalization for this purpose is avoided, and the postpartum hospitalization prolonged but slightly, if at all. It, therefore, has important economic aspects. The disadvantages of the development of infection or failure to sterilize are mostly, but not entirely, due to poor selection of cases and mistakes in technique.

Studies on the Bacteriology of the Postpartum Uterus

Some of the classical contributions to the study of the bacteriology of the puerperium, such as those of Schottmüller,[18] Schwarz and Dieckmann,[19] Colebrook and Hare[20] and others, have been done in relation to puerperal sepsis. In forming a judgment as to the proper time to carry out this procedure or any manipulation of the puerperal uterus, it is necessary to consider the bacteriology of the normal, newly delivered uterus. Only in this way can infections such as phlebitis and thrombosis be avoided. With that in mind, we attempted a study to determine the time of bacterial invasion of the uterus after delivery. Uterine cultures were taken on 100 patients who had delivered through the natural passages, and none of the patients was operated upon. There was no selection of patients except that only nonfebrile patients were included in this series. Only three patients had a temperature as high as 99.4° F. and on only one occasion. Only one culture was taken on each patient, and no patient had fever after taking the culture. Uterine cultures were taken on patients in groups of 10 at the end of two, four, six, eight, and ten hours, and at the end of the first, second, third, fourth, and fifth days.

The Technique of Taking Cultures

With the patient lying on her back, the perineum was cleansed with sterile water. With the legs flexed, the labia were separated and a bivalve speculum inserted to expose the cervix. A modified Little[21] tube was inserted through the cervix into the uterine cavity without touching anything on the way. The Little tube had been sterilized while wrapped in heavy paper. The tube was unwrapped, the culture taken, the tube rewrapped and placed in a sterile, covered, porcelain container, and taken to the laboratory. Immediately upon receipt in the laboratory, the Little tube was removed from its sterile paper wrapping, flamed, and the contents allowed to run into a tube of sterile saline Aerobic and anaerobic cultures were completed on all specimens. The resultant suspension was then planted for study as follows:

Aerobic Culture.—A tube of veal and brain infusion broth, a blood agar plate (human blood being used), and an eosin-methylene blue agar plate were incubated at 37° C. and examined at the end of twenty-four and forty-eight hours. If negative, the plates were discarded and the broth examined again five days after taking the culture before the specimen was declared negative. If, at this time, the broth was positive, plates were streaked from the broth.

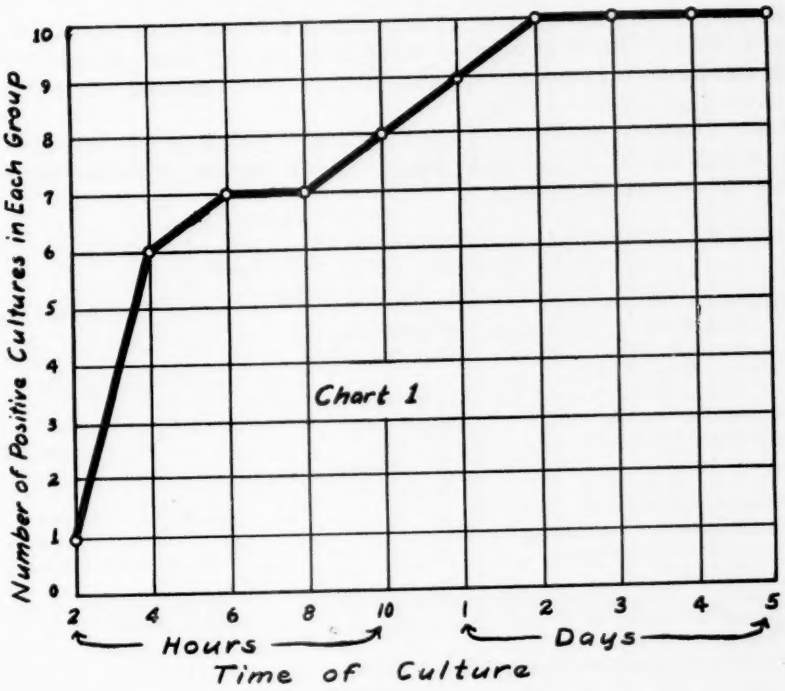

Chart 1.

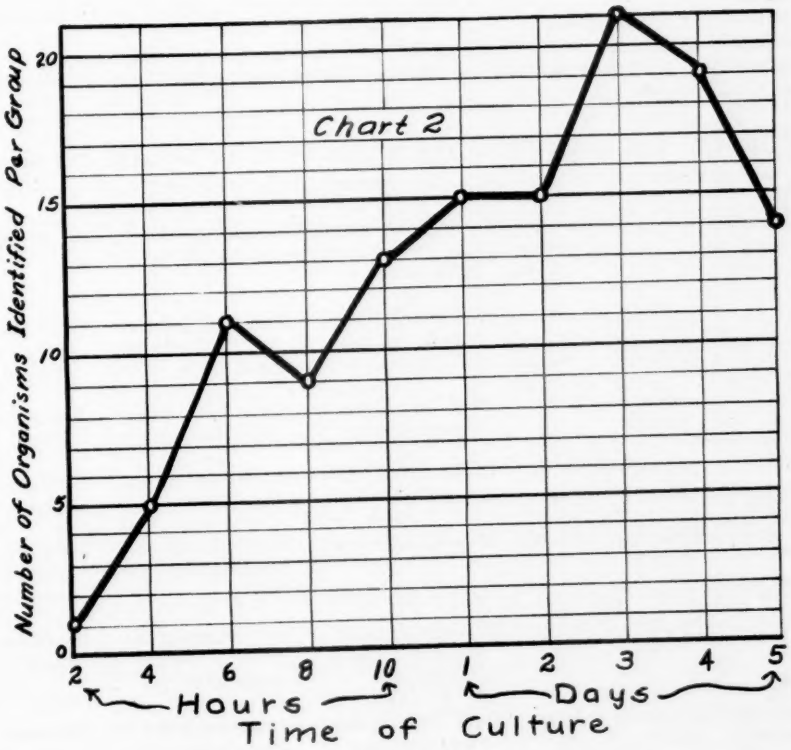

Chart 2.

Anaerobic Culture.—A tube of broth and a blood plate were incubated for forty-eight hours under anaerobic conditions, using the phosphorus method, and then examined. If negative, the broth was re-examined when five days old before being discarded.

Carbon Dioxide Culture.—Chocolate agar plates were liberally streaked and examined after forty-eight hours under carbon dioxide tension. The method of Wadsworth was used.

TABLE III. PERCENTAGE OF OCCURRENCE OF ORGANISMS IN POSITIVE CULTURES
123 ORGANISMS FOUND IN 87 CASES

Anaerobic *Streptococci*		39 per cent
hemolytic	20 per cent	
nonhemolytic	19 per cent	
Aerobic *Staphylocci*		17 per cent
hemolytic	3 per cent	
nonhemolytic	14 per cent	
Aerobic *Streptococci*		15 per cent
hemolytic	6 per cent	
nonhemolytic	9 per cent	
Escherichia coli		14 per cent
Gram positive sporulating bacilli		8 per cent
Bacterium aerogenes		6 per cent
Diphtheroids		6 per cent
Anaerobic gram negative sporulating bacilli		5 per cent
Hemophilic bacilli		3 per cent
Neisserian group		3 per cent
Anaerobic hemolytic *Staphylococcus aureus*		2 per cent
Bacterioides		2 per cent
Monilia		1 per cent
Actinomyces		1 per cent
Micrococcus tetragenus		1 per cent

Saprophytic organisms were found in 19 per cent of the positive cases, but in only 5 per cent were they found alone. In all other instances they were found in association with one or more pathogens.

TABLE IV. ORGANISMS FOUND AND NUMBER OF TIMES ISOLATED PER GROUP

(Part 1)

		Hemophilic bacillus, probably *H. influenzae*	Nonhemolytic *Staph. albus*	*B. aerogenes*
		(1)	(1)	(3)
		Nonhemolytic *Staph.* aureus, anaerobic	Gram neg. sporulating bacillus, anaerobic	Gram neg. sporulating bacillus, anaerobic
		(2)	(1)	(2)
	Actinomyces nocardia	Beta hemolytic *Streptococcus*	Beta hemolytic *Streptococcus*	Nonhemolytic *Staph. aureus*
	(1)	(1)	(1)	(1)
	Nonhemolytic *Streptococcus*	Diphtheroid, unidentified	*Bacterioides*, unidentified	Nonhemolytic *Staph. albus*
	(1)	(1)	(2)	(2)
	Hemolytic *Staph. aureus*	*Monilia albicans*	Gram positive sporulating bacillus	Beta hemolytic *Streptococcus*, anaerobic
	(1)	(1)	(1)	(1)
	Nonhemolytic *Staph.* aureus	Nonhemolytic *Streptococcus* anaerobic	Beta hemolytic *Streptococcus*, anaerobic	Nonhemolytic *Streptococcus*,
	(1)	(3)	(2)	(2)
Beta hemolytic *Streptococcus*, anaerobic	Alpha hemolytic *Streptococcus*, anaerobic	Beta hemolytic *Streptococcus* anaerobic	Nonhemolytic *Streptococcus*, anaerobic	Gram positive sporulating bacillus
(1)	(1)	(2)	(1)	(2)
2 hours	4 hours	6 hours	8 hours	10 hours

TABLE IV—CONT'D—*(Part 2)*

			Hemolytic *Staph. albus* (1)	
			Diphtheroid, unidentified (1)	
			Nonhemolytic *Staph. aureus* (1)	
			Beta hemolytic *Streptococcus*, anaerobic (2)	
		B. aerogenes (1)	Nonhemolytic *Staph. albus* (1)	
Nonhemolytic *Staph. albus* (1)		Nonhemolytic *Staph. aureus* (2)	Nonhemolytic *Streptococcus* (1)	*E. Coli* (2)
E. Coli (2)		Nonhemolytic *Streptococcus* (3)	*E. Coli* (3)	*B. xerosis* (2)
Nonhemolytic *Streptococcus* (2)	*E. Coli* (3)	*B. xerosis* (1)	*B. subtilis* (1)	*B. aerogenes* (2)
Beta hemolytic *Streptococcus* (1)	Nonhemolytic *Streptococcus* (1)	*E. Coli* (4)	Micrococcus tetragenus (1)	Hemolytic *Staph. aureus* (1)
Beta hemolytic *Streptococcus*, anaerobic (2)	Nonhemolytic *Streptococcus*, anaerobic (4)	Diphtheroid, unidentified (1)	Nonhemolytic *Streptococcus* anaerobic (3)	Alpha hemolytic *Streptococcus* (1)
Nonhemolytic *Streptococcus*, anaerobic (2)	Beta hemolytic *Streptococcus*, anaerobic (2)	Nonhemolytic *Staph. albus* (1)	A. hemolytic *Streptococcus*, anaerobic (1)	Beta hemolytic *Streptococcus* (1)
Nonhemolytic *Staph. aureus* (2)	Nonhemolytic *Staph. aureus* (1)	Beta hemolytic *Streptococcus*, anaerobic (5)	Member of *Neisseria* group (1)	Nonhemolytic *Streptococcus* (1)
Gram positive sporulating bacillus (1)	Gram positive sporulating bacillus (2)	Nonhemolytic *Streptococcus*, anaerobic (1)	Gram negative sporulating bacillus (1)	Nonhemolytic *Streptococcus*, anaerobic (3)
Gram negative sporulating bacillus anaerobic (1)	Alpha hemolytic *Streptococcus* (1)	Member of *Neisseria group* (1)	Hemophilic bacillus, probably *H. influenzae* (1)	A. hemolytic *Streptococcus*, anaerobic (1)
Hemophilic bacillus, probably *H. ducrey* (1)	Member of *Neisseria* group (1)	Gram positive sporulating bacillus (1)		
1 day	2 days	3 days	4 days	5 days

A direct smear of each specimen was made after inoculation. Eight per cent of the cases showed bacteria on such examination, none of which was less than twenty-four hours post partum.

Special procedures used for identification of bacteria were as follows:

1. Bile solubility and capsule staining to differentiate *Streptococcus viridans* from the *Pneumococcus*. No *pneumococci* were found.

2. Oxidase dye test to confirm the presence of colonies of *Neisseriae*.

3. Coagulase test on *Staphylococci*. No *Staphylococci* were found with the ability to coagulate plasma.

4. Sugar fermentation reactions were used for the differentiation of diphtheroids, *Monilia*, and *Actinomyces*.

Results

In 100 uterine cultures 87 were positive, 13 negative, and the latter occurred only among the cultures which were obtained during the first few hours.

Chart 1 gives eloquent evidence as to the time of bacterial invasion of the uterus after delivery. It will be noted that at the end of two hours, only 1 in 10 cultures was positvie. At the end of four hours, 6 in 10 cultures were positive. At the end of six and again at eight hours, 7 in 10 cultures were positive. At the end of ten hours, 8 cultures were positive, while at the end of the first day, 9 of 10 were positive, and from the second to the fifth days all—that is, 40 consecutive cultures—were positive. It will be noted in Chart 2 that the number of organisms identified similarly increases up to the end of the third day and then the number decreases. It is possible that by the end of the third day, local and general immunities are beginning to become effective, but although the number of organisms had decreased, the cultures of the fourth and fifth days were markedly positive.

Table III illustrates that in the 100 uterine cultures taken, 123 organisms were found in the 87 positive cultures. Of the 123 organisms, 39 per cent were anaerobic *Streptococci,* 17 per cent aerobic *Staphylococci,* 15 per cent aerobic *Streptococci,* and 14 per cent *Escherichia coli.* It should be noted that although saprophytic organisms were found in 19 per cent of the positive cultures, they were found alone in only 5 per cent. Otherwise, they were always in association with one or more pathogens.

Table IV demonstrates the bacteria and the number of times which each was identified in each time group of these 100 uterine cultures. The least number was, of course, at two hours, and the greatest variety cultured was at the end of four days.

Summary

The performance of early postpartum sterilization on nonfebrile patients has already stood the test of time. A group of early postpartum sterilizations from the Peiping Union Medical College, Peking, China, and the University of Tennessee College of Medicine, Memphis has been reported with studies on the bacteriology of the puerperal uterus. Studies on the normal postpartum uterus show that bacterial invasion occurs soon after delivery. It is clear that in many instances it might be necessary to wait a few hours after delivery before such a procedure is undertaken, but if the patient's condition is such that one should wait many hours, it is questionable as to whether it should be done at all, and certainly not after the first day. These bacteriologic studies also support the well-known clinical fact that the removal of membranes or fragments of placental tissue from the uterus shortly after delivery is relatively safe, whereas, the same procedure after the first postpartum day may be a dangerous intervention. With the patient in good condition, she is better protected by carrying out such a procedure in the early postpartum period. The optimum time to perform postpartum sterilization is from one to two hours after spontaneous delivery, which means that the period of probable postpartum hemorrhage is over, and the period of probable infection has not yet begun.

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Discussion

DR. FRED L. ADAIR, Chesterton, Ind.—In discussing any operative procedure one should have three thoughts in mind: first, is it necessary; second, is it relatively safe in relation to the purpose to be accomplished; and, third, is it effective? It is generally agreed that there are certain conditions affecting women which make pregnancy a serious hazard to health and life, and where future pregnancies should be avoided.

The conditions would seem to be recognized in Dr. Whitecre's and also in the series of Dr. Brown and me. In a subsequent series collected by Dr. Dieckmann for another purpose, the indications remain practically the same, except that multiparity becomes somewhat more important. The indications regarding multiparity appear to be more economic and sociological than medical.

This operation affords one of the means of avoiding future pregnancies in those women where pregnancy constitutes a hazard to her life or health. The main hazard is from the possibility of infection. Originally, we attempted to distinguish between immediate, early, and late procedures. The first was done immediately following delivery, the second within the first twenty-four hours, and the last at some later period in the puerperium. It is well known, of course, that there is a bacterial ascending infection of the genital tract during labor itself, so it would seem that we should consider that factor in relation to infection. We should evaluate not only the actual labor itself, but the conduct of labor and the contraindications to the procedure. For reasons which seemed logical, we have carried out the early, or twenty-four hour, procedure. The bacteriologic studies presented indicate that from the point of the bacteriologic invasion of the genital tract this is the preferable time.

One of our contraindications was an abnormal labor. It should be kept in mind that the concentration of bacteria and the relation to the amount of lochial discharge may modify the number and variety of bacteria recovered by cultural methods. However, the main conclusion stands that the bacteria increase progressively in number and variety as the puerperium proceeds, and gradual involution leads to their decrease and elimination. While these organisms are obtained from the genital tract for technical reasons, it is very difficult to prove that they come from the uterine cavity itself.

The morbidity from this 24-hour procedure has been low and the mortality is nil. A point of importance is that failure in about 5 per cent of the cases is higher than in those patients who had tubal ligation when the uterus was not about to undergo involution. It may be due to the process of involution or also, possibly, to some imperfect technique. The operation is simple, but meticulous care is necessary to avoid subsequent fistulous formation or a restoration of the tubal lumen.

DR. EDWARD D. ALLEN, Chicago, Ill.—My discussion of this subject will have to be largely theoretical, because we have had no immediate experience with postpartum sterilization in my service. Sterilizations at the time of delivery have been limited to those indi-

cated following cesarean section or therapeutic abortion. Sterilization has not been used as a deciding indication for cesarean section, except in a very few borderline cases in whom previous obstetrical history has indicated that another pregnancy would probably occur before an operation during the early postpartum period could be done. If this or a similar type of patient can be safely delivered through the vagina, we believe they may be the only ones in which sterilization during the early puerperium is indicated.

We have not been able to prognosticate a normal puerperium accurately enough that we have felt justified in adding a laparotomy, however simple, to the risks already incurred by delivery. Some of our mortalities and many of the severe morbidities have occurred following uncomplicated delivery. In view of the results just reported by Dr. Whitacre, it would seem that in otherwise normal cases we are operating upon patients in whom a potential focus of infection will occur in twenty-four or forty-eight hours. It seems like crossing the railroad track when the red light is swinging; most often we will make it, but sometimes we will not. I do not know of anywhere else in surgery where we would choose these unfavorable possibilities.

Our departmental policy has been to delay sterilization until the pelvic organs have returned to normal except in those instances where the patient is already pregnant and therapeutic abortion followed by sterilization is indicated, especially in those patients in whom we have reason to believe that another pregnancy will occur if the sterilization is too long delayed. The morbidity and mortality in this pregnant group have been higher than in the nonpregnant series. The incidence of complications has increased with the duration of pregnancy. A more critical analysis of our results which is now being undertaken seems to indicate that in the future we will only undertake abortion and sterilization together for those unusual circumstances mentioned above. The results obtained in Dr. Whitacre's excellent study, I believe, will strengthen this decision.

We believe that sterilization by the vaginal route is safer than by the abdominal approach. In addition, if performed during the nonpuerperal state, it safely allows the additional procedures for cure of other pelvic complaints so commonly found in the patient needing sterilization. We have not included in these few statistics those cases of vaginal hysterectomy, of which there are a considerable number, done primarily for sterilization, but also to rid the patient of a bleeding painful uterus or partial prolapse. Eighty-nine of our sterilizations were done as a step in extensive plastic repair when hysterectomy was not indicated and the patient still in the childbearing age.

During the years from 1930 to 1944 there have been done on our service 210 vaginal sterilizations. One hundred and thirty-six of these were done on the involuted uterus and 74 following therapeutic abortion.

There has been one death which occurred forty-five days postoperatively from cerebral embolism in a patient who had been coincidentally aborted for endocarditis. Pregnancy occurred subsequently in three of these pregnant patients; all following cornual resection. As far as we can determine, no pregnancy has followed the other procedures, although no exact follow-up study has been made. In our hands, the smoothest results have been obtained by the modified Pomeroy. A loop in the midportion of the tube is crushed, tied with chromic catgut, and the looped portion of the tube removed. It is a simple, quickly done procedure, and statistically is as accurate as any procedure thus far reported in numbers large enough to be evaluated.

Eighty-three patients were sterilized by cornual resection, six had defundectomies, and in ten of the pregnant patients the products of conception were removed by hysterotomy and the tubal continuity interrupted by a modified Pomeroy. Twenty-five patients were aborted at 4 to 7 weeks term, 44 to 8 to 10 weeks, and 5 at 11 to 14 weeks. The average hospital stay of these patients was eight days. While those in the nonpregnant group required only 6.3 days. We are of the opinion that this length of stay in the hospital to undergo a relatively painless and safe operation is not sufficient indication to add even the minimal risk of abdominal sterilization to a newly delivered woman, unless her mentality or marital relationship will not permit of further delay.

DR. E. L. KING, New Orleans, La.—We have occasion at the New Orleans Charity Hospital to do this operation very frequently. Our chief indication is in the Negro multipara with cardiovascular disease. There are some other indications also, but the largest single group fall in that category. We have had 218 cases upon whom postpartum sterilization has been done in the past several years.

The time limit is somewhat different from that of Dr. Whitacre, but it has not seemed to interfere with the results obtained. We have not sterilized very many of these patients within the first few hours, the chief reason being not so much clinical or bacteriologic, but practical. We feel that it is necessary in these patients to obtain the written consent of both husband and wife. Many of these women of the renal-vascular group come in in labor or in a severely toxic state, and many of them are delivered within a few hours or a day after admission. Frequently it is a matter of several days before we can get the necessary papers signed. Besides that, to protect ourselves from criticism, we have to get the medical service of the Institution to agree that the patient should be sterilized, and that also takes time. So our sterilizations have taken place over several days to a week.

We have not had any mortality, but we realize, of course, that we are working with a uterus that has bacterial contamination. By tying an extra ligature around the tube on each side of the ligated loop, we think that we have improved the method. We can say that one patient has returned pregnant after this operation. The others have not been followed up.

DR. WHITACRE (Closing).—In regard to Dr. Allen's remarks, this procedure was intended in a special group of cases to avoid cesarean section which, it is clear, carries a low but definite mortality. Also, it avoids therapeutic abortion in some of these patients in the future.

It should be mentioned in relation to Dr. King's suggestion of extra ligatures in the tube, that the one most proximal to the uterus is the important one, for, if the serosa is broken, it might result in a tuboperitoneal fistula and, therefore, failure, regardless of other ligatures.

We have no intention of being dogmatic, but this study on the bacteriology of the puerperal uterus indicates this time when any manipulation of the puerperal uterus can be carried out with reasonable safety.

(As it was not possible to include all of the papers presented at the meeting, the remainder will appear in the January number of the JOURNAL.*)*

Necrology

DR. JOHN A McGLINN, associate professor of gynecology in the Postgraduate School of the University of Pennsylvania (retired), consultant to the Philadelphia General Hospital, the Fitzgerald Mercy Hospital, Phipps Institute, and St. Luke's Hospital, Vice-President of the American Gynecological Society in 1936, past President of the Philadelphia Medical and the Philadelphia Obstetrical Societies, Fellow of the American College of Surgeons, died on Nov. 29, 1946, in Philadelphia, at the age of 75 years.

Items

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 7, 1947.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held June 1 to 7, 1947, at Pittsburgh, Pa. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pa.

The following physician has completed all requirements for certification by this Board, and is included in the list of diplomates: Dr. Herschel Frank Connally, 1305 Amicable Bldg., Waco, Texas.

The International Congress of Obstetrics and Gynecology

The Congress will be held in Dublin, Ireland, during the week beginning July 7, 1947, to celebrate the Bicentenary of the Rotunda Hospital. Representatives from all parts of the world have signified their intention to participate in the presentation of an elaborate program which includes addresses and discussions on the history of midwifery, puerperal sepsis, eclampsia, sterility, puerperal mortality, and obstetric shock. Messrs. Thomas Cook and Son, Ltd., are the authorized travel agency and also accept registrations for the Congress. The Honorary Secretary is Mr. G. F. Klingner, Rotunda Hospital, Dublin.

INDEX TO VOLUME 52

AUTHORS INDEX*

A

AABERG, MONRAD E., Ancylostomiasis and hypoproteinemia complicated by pregnancy, 854

ABRAMS, ARCHIE A., AND ABRAMS, SOL. B., Successful treatment of hydramnios with ammonium chloride, 299

ABRAMS, SOL. B. (WITH ABRAMS, ARCHIE A.), Successful treatment of hydramnios with ammonium chloride, 299

ADRIANI, JOHN (WITH PARMLEY, RAY T.), Saddle block anesthesia with nupercaine in obstetrics, 636

ANDREWS, C. J., AND NICHOLLS, RICHARD B., Recurrent placenta previa, 347 (Correspondence)

B

BARTELMEZ, G. W. (WITH ROSSMAN, I.), Delayed ovulation, a significant factor in the variability of the menstrual cycle, 28

BEECHAM, CLAYTON T., Conservative surgery in endometriosis, 707

BELSON, MAURICE O., The Rh factor in obstetrics, 106

BENSON, RALPH C., The treatment of acute postpartum thrombophlebitis of the lower extremity by continuous caudal anesthesia, 830

BERNSTEIN, PHINEAS, SCHOENECK, FERDINAND J., AND ZERNER, HERBERT. Government sponsorship of a maternity program in wartime, 510

BIANCO, JOHN J., AND FAVORITE, GRANT O., Granulosa-cell tumor of the ovary, 677

BONSNES, R. W. (WITH STANDER, H. J., AND STROMME, W. B.), Late postpartum eclampsia, 765

BUNKIN, IRVING A. (WITH FALK, HENRY C.), A study of 500 vaginal hysterectomies, 623

BURT, OLAN P. (WITH SILBERNAGEL, WYNNE M.), Pyridoxine in nausea and vomiting of pregnancy, 173 (Correspondence)

BUTLER, EDWIN M., AND HOWARD, VIRGINIA, Multiple pregnancy with early abortion of one fetus, 163

C

CAMPBELL, ZEPH B., A report on 2,798 vaginal hysterectomies, 598

CARR, CLAIRE E. (WITH NORA, ERNEST), Umbilical accessory liver, 330

CHEEK, DAVID B., AND DAVIS, JAMES E., Pathologic findings in genital bleeding two or more years after spontaneous cessation of menstruation, 756

CHESLEY, LEON C., COSGROVE, S. A., AND PREECE, JOHN, Hydatidiform mole, with special reference to recurrence and associated eclampsia, 311

COHN, ALFRED, GRUNSTEIN, ISAAK, AND HEATON, C. E., The persistence of the gonococcus in the female adnexa, 83

COLE, JOHN TOTTERDALE, Maternal obstetric paralysis, 372

COLEMAN, FRANK C. (WITH COPLAND, SIDNEY M.), Bilateral concomitant fibroma and serous cystadenoma of the ovary, 141

COLLINS, CONRAD G., AND NELSON, EDWARD W., Phlebothrombosis and thrombophlebitis in gynecology and obstetrics, 946

COMPTON, J. ROY, A new introducer and cannula for obstetric and surgical cases suitable for caudal analgesia, 503

CONTI, EUGENE A., AND GLENN, JOHN W., Hemolytic disease associated with the Rh factor in twin pregnancies, 446

COPLAND, SIDNEY M., AND COLEMAN, FRANK C., Bilateral concomitant fibroma and serous cystadenoma of the ovary, 141

CORNELISON, J. L., JOHNSON, E. A., AND FISHER, W. M., Bacteriology of the oronasal cavity of the newborn, 797

CORYELL, MARGARET (WITH PRATT, J. P., RODERUCK, CHARLOTTE, AND MACY, ICIE G.), Composition of the human placenta, III. Vitamin content, 783

COSGROVE, S. A. (WITH CHESLEY, LEON C., AND PREECE, JOHN), Hydatidiform mole, with special reference to recurrence and associated eclampsia, 311

—, AND WATERS, E. G., An evaluation of extraperitoneal cesarean section, 237

COULTON, DONALD (WITH SEWALL, C. WESLEY), Manual removal of the placenta; a benign procedure, 564

CURTIS, ARTHUR C., AND MORROW, GRANT, The treatment with massive arsenotherapy of early syphilis complicated by pregnancy, 284

CURTIS, ARTHUR H., Another case of arrhenoblastoma, 128

—, The origin of adrenal-like tumor of the ovary, 115

D

DANFORTH, W. C., Total abdominal hysterectomy, 218

DANNREUTHER, WALTER T., Therapeutic abortion in a general hospital, 54

DAVENPORT, J. W., JR., (WITH KING, E. L.), Some clinical aspects of the Rh factor in obstetrics, 917

DAVIES, JOSHUA (WITH MILLEN, ROBERT S.), See-saw resuscitator for the treatment of asphyxia in the newborn, 508

DAVIS, JAMES E. (WITH CHEEK, DAVID B.), Pathologic findings in genital bleeding two or more years after spontaneous cessation of menstruation, 756

DIECKMANN, WILLIAM J., Fetal mortality in breech delivery, 349

DIEHL, WILLIAM K., AND HAUGHT, JOHN S., Sarcoma of the vagina, 302

DILL, L. V., AND MAIDEN, ROBERT M., The electrical potentials of the human uterus in labor, 735

DINDIA, ANTHONY H., AND TURCOTTE, VINCENT J., Extrauterine pregnancy, 321

*July, pp. 1-178; August, pp. 179-348; September, pp. 349-528; October, pp. 529-706; November, pp. 707-880; December, pp. 881-1066.

DOBRZYNSKI, F. A. (WITH KUSHNER, DAVID H.), Abdominal pregnancy with placenta attached to the spleen, 160

DOUGLAS, H. GORDON, An unusual case of rupture of the uterus with massive hemorrhage, 135

DURBURG, JOHN R., Chorionepithelioma in an 18-year-old primigravida, 484

E

ELLER, WILLIAM C., Cerebrovascular complications of pregnancy, 488

— (WITH MENGERT, WILLIAM F.), Graphic portrayal of relative pelvic size, 1032

EVERETT, HOUSTON S. (WITH JONES, GEORGIANNA SEEGAR), Arrhenoblastoma of the ovary, with a report of two cases, 614

F

FALK, HENRY C., Interpretation of the pathogenesis of pelvic infection as determined by cornual resection, 66

—, AND BUNKIN, IRVING A., A study of 500 vaginal hysterectomies, 623

FARELL, DAVID M. (WITH SCHEFFEY, LEWIS C., THUDIUM, WILLIAM J., AND HAHN, GEORGE A.), Controversial factors in the management of fundal carcinoma, 529

FARRIS, EDMOND J., A test for determining the time of ovulation and conception in women, 14

FAVORITE, GRANT O. (WITH BIANCO, JOHN J.), Granulosa-cell tumor of the ovary, 677

FISHER, W. M. (WITH CORNELISON, J. L., AND JOHNSON, E. A.), Bacteriology of the oronasal cavity of the newborn, 797

FLICKINGER, F. MILES, AND MASSON, JAMES C., Lipomas of the broad ligament extending beyond the confines of the pelvis, 681

G

GLENN, JOHN W. (WITH CONTI, EUGENE A.), Hemolytic disease associated with the Rh factor in twin pregnancies, 446

GOLD, SIMON, AND KEARNS, P. J., Cystic adenomyosis of the uterus, 840

GOLDFARB, WILLIAM S., AND VEPROVSKY, EDWARD C., Acute suppurative parotitis complicating pregnancy at term, 147

GOLDSTINE, MARK T., Arrhenoblastoma of the ovary, 123

GORDON, CHARLES A., The Manchester operation, with special reference to parturition and complete prolapse, 228

GORDON, JULES D., Sliding hernia of the Fallopian tube, 336

GOTTSCHALK, ROBERT H., Respiration during the first hour of life, 651

GREENBERG, EMANUEL M., The fourth stage of labor, an account of the physiology and clinical aspects of the postpartum uterus during the first postplacental hour, 746

GRUNSTEIN, ISAAK (WITH COHN, ALFRED, AND HEATON, C. E.), The persistence of the gonococcus in the female adnexa, 83

GUSBERG, S. B., Prolapse of the umbilical cord, 826

— (WITH WATSON, B. P.), Prevention and treatment of carcinoma of the vulva, 179

GUTERMAN, HENRY S., The Guterman pregnancy test, 174 (Correspondence)

GUYER, HERBERT B. (WITH TAYLOR, HOWARD C., JR.), A seven-year history in early cervical cancer, 451

—, AND HEATON, CLAUDE E., The fetal risk in breech delivery, 362

H

HAHN, GEORGE A. (WITH SCHEFFEY, LEWIS C., THUDIUM, WILLIAM J., AND FARELL, DAVID M.), Controversial factors in the management of fundal carcinoma, 529

HAMMOND, HOWARD, JR., AND NUZUM, THOMAS O., Adult Mediterranean anemia complicated by pregnancy, 686

HARRIS, C. M., AND LEVITON, L. R., Bilateral simultaneous tubal pregnancy, 492

HAUGHT, JOHN S. (WITH DIEHL, WILLIAM K.), Sarcoma of the vagina, 302

HAWKES, STUART Z., Enterouterine fistula, with a review of the literature and report of an unusual case, 150

HEADINGS, DONALD M., AND PALMER, RUFUS E., III, Relation of early rising to morbidity in cesarean section, 661

HEATON, C. E. (WITH COHN, ALFRED, AND GRUNSTEIN, ISAAK), The persistence of the gonococcus in the female adnexa, 83

— (WITH GUYER, HERBERT B.), The fetal risk in breech delivery, 362

HELSEL, E. V., A review of one hundred cases of ovarian cancer, 435

HENDERSON, CHARLES W. (WITH MILLER, NORMAN F.), Corpus carcinoma, a study of three hundred twenty-two cases, 894

HENDERSON, D. NELSON, Endolymphatic stromal myosis, 1000

HESS, CATHERINE B. (WITH SHARKEY, JOHN A.), The effect of essential hypertension on pregnancy, 672

HESSELTINE, H. CLOSE, AND THELEN, CHRISTINE, Sulfonamides as a prophylactic agent in conjunction with cesarean section, 813

HOFMEISTER, F. J., Large ovarian cyst, 135

HOLMSTROM, E. G. (WITH MCLENNAN, C. E.), Abdominal wall fibroma (urachal?) simulating ovarian cystoma, 154

HOTCHKISS, ROBERT S. (WITH MACLEOD, JOHN), Semen analysis in 1,500 cases of sterile marriage, 34

HOWARD, VIRGINIA (WITH BUTLER, EDWIN M.), Multiple pregnancy with early abortion of one fetus, 161

HUNT, ARTHUR B. (WITH TREUSCH, JEROME V., AND ROUSUCK, A. ASHLEY), Infrequency of carcinoma of the uterine cervix among Jewish women, 162

HUNT, MARJORIE (WITH PAGE, ERNEST W., AND LUCIA, S. P.), The antepartum prediction of hemolytic disease of the newborn, 794

I

INGERSOLL, FRANCIS M. (WITH MEIGS, JOE V.), Thrombophlebitis and phlebothrombosis in gynecologic patients; the prophylaxis, recognition, and treatment, 938

INGRAM, C. H., JR., Some observations upon the Rh factor in pregnancy, 440

J

JAVERT, CARL T., Combined procedure for anteroversion of retroverted uteri, 865

—, Traveling in pregnancy, 347 (Correspondence)

JOHNSON, E. A. (WITH CORNELISON, J. L., AND FISHER, W. M.), Bacteriology of the oronasal cavity of the newborn, 797

JOHNSON, HERMAN W., The clinical diagnosis of varying degrees of uterine contraction rings, 74

JONES, GEORGIANNA SEEGAR, AND EVERETT, HOUSTON S., Arrhenoblastoma of the ovary, with a report of two cases, 614

K

KAMINSKI, CHESTER A. (WITH SANES, S.), Spontaneous rupture of the liver in eclampsia with fatal hemoperitoneum, 325

KAUCHER, MILDRED (WITH PRATT, J. P., MOYER, ELSIE, RICHARDS, ALLEN J., AND WILLIAMS, HAROLD H.), Composition of the human placenta. II. Lipid content, 665

— (WITH PRATT, J. P., RICHARDS, ALLEN J., WILLIAMS, HAROLD H., AND MACY, ICIE G.), Composition of the human placenta. I. Proximate composition, 402

KEARNS, P. J. (WITH GOLD, SIMON), Cystic adenomyosis of the uterus, 840

KELBERG, MELVIN R., AND RANDALL, J. H., Torsion of adnexal tumors and its relation to surgical emergency, 464

KENNEDY, WILLIAM T., Retention catheter, 506

—, The muscle of micturition, its role in the sphincter mechanism with reference to incontinence of the female, 206

KING, ARTHUR G., Early puerperal rising, 657

KING, E. L., AND DAVENPORT, J. W., JR., Some clinical aspects of the Rh factor in obstetrics, 917

KLEIN, JOSEPH, The relationship of maternal weight gain to the weight of the newborn infant, 574

KROGER, WILLIAM S., The treatment of psychogynecic disorders by hypnoanalysis, 409

KUDER, ALBERTA (WITH MARCHETTI, ANDREW A., AND KUDER, KATHERINE), A clinical evaluation of ectopic pregnancy, 544

KUDER, KATHERINE (WITH MARCHETTI, ANDREW, A., AND KUDER, ALBERTA), A clinical evaluation of ectopic pregnancy, 544

— (WITH STROMME, WILLIAM B.), Heart disease in pregnancy, 264

KUKRAL, ALBERT J. (WITH PENNELL, MELVIN T), An unusual case of holoacephalus, 669

KUSHNER, DAVID H., AND DOBRZYNSKI, F. A., Abdominal pregnancy with placenta attached to the spleen, 160

KUSHNER, J. IRVING, AND WAHRSINGER, PHILIP B., The Kielland forceps for use in the occipitoposterior and occipitotransverse positions, 110

L

LANG, WARREN R. (WITH SCHEFFEY, LEWIS C., AND NUGENT, FRED B.), Clinical and pathologic aspects of primary sarcoma of the uterine tube, 904

LANGMAN, LOUIS, AND TAYLOR, HOWARD C., JR., The selection of forceps for midpelvic arrest of the vertex, 773

LATOUR, J. P. A. (WITH PHILPOTT, N. W., AND VANDORSSER, G. J. E.), Review of cases of Rh iso-immunization during the past five years in the Royal Victoria Montreal Maternity Hospital, 926

LEFF, BENJAMIN, Air cystoscope with a universal handle and external light, 505

LEVENTHAL, MICHAEL L., AND SOLOMON, ERNST M., Pelvic endometriosis as a cause of hydronephrosis, 692

LEVITON, L. R. (WITH HARRIS, C. M.), Bilateral simultaneous tubal pregnancy, 492

LOCK, FRANK R., AND MYERS, RICHARD T., Endometriosis in association with pregnancy, 556

LOEB, LAURA (WITH WHITACRE, FRANK E., AND LOEB, WALTER M., JR.), The time for postpartum sterilization, 1041

LOEB, WALTER M., JR. (WITH WHITACRE, FRANK E., AND LOEB, LAURA), The time for postpartum sterilization, 1041

LOESER, ALFRED A., Lactobacillus therapy in vaginitis due to trichomonas, 879 (Correspondence)

LOUGHRAN, CHARLES H., Weight control diet, and fluid balance in pregnancy, 42

LUCIA, S. P. (WITH PAGE, ERNEST W., AND HUNT, MARJORIE), The antepartum prediction of hemolytic disease of the newborn, 794

LUIKART, RALPH, High protein, low caloric diet for the prevention of toxemia of pregnancy, 428

M

MACDONALD, JAMES F., AND MASTERS, V. E., Bilateral simultaneous tubal pregnancy, 850

MACLEOD, JOHN, AND HOTCHKISS, ROBERT S., Semen analysis in 1,500 cases of sterile marriage, 34

MACY, ICIE G. (WITH PRATT, J. P., KAUCHER, MILDRED, RICHARDS, ALLEN J., AND WILLIAMS, HAROLD H.), Composition of the human placenta. I. Proximate composition, 402

— (WITH PRATT, J. P., RODERUCK, CHARLOTTE, AND CORYELL, MARGARET), Composition of the human placenta. III. Vitamin content, 783

MAIDEN, ROBERT M. (WITH DILL, L. V.), The electrical potentials of the human uterus in labor, 735

MALONE, CHARLES M., Critical study of 390 major gynecologic surgical procedures, 291

MARCHETTI, ANDREW, KUDER, KATHERINE, AND KUDER, ALBERTA, A clinical evaluation of ectopic pregnancy, 544

MASSON, JAMES C. (WITH FLICHINGER, F. MILES), Lipomas of the broad ligament extending beyond the confines of the pelvis, 681

MASTERS, V. E. (WITH MACDONALD, JAMES F.), Bilateral simultaneous tubal pregnancy, 850

MCLENNAN, CHAS. E., Further observations on capillary filtration rates in pregnancy, 837

—, AND HOLMSTROM, E. G., Abdominal wall fibroma (urachal?) simulating ovarian cystoma, 154

MEIGS, JOE V., AND INGERSOLL, FRANCIS M., Thrombophlebitis and phlebothrombosis in gynecologic patients; the prophylaxis, recognition, and treatment, 938

MENDELSON, CURTIS L., The aspiration of stomach contents into the lungs during obstetric anesthesia, 191

MENGERT, WILLIAM F., AND ELLER, WILLIAM C., Graphic portrayal of relative pelvic size, 1032

MICHAELS, JACK P. (WITH NELSON, EDWARD W.), Acute postparptum necrosis of the anterior hypophysis, 817

MILLEN, ROBERT S., AND DAVIES, JOSHUA, See-saw resuscitator for the treatment of asphyxia in the newborn, 508

MILLER, NORMAN F., AND HENDERSON, CHARLES W., Corpus carcinoma, a study of three hundred twenty-two cases, 894

MOORE, JOHN H., Environment in obstetrics, 993

MORROW, GRANT (WITH CURTIS, ARTHUR C.), The treatment with massive arsenotherapy of early syphilis complicated by pregnancy, 284

MOYER, ELSIE (WITH PRATT, J. P., KAUCHER, MILDRED, RICHARDS, ALLEN J., AND WILLIAMS, HAROLD H.), Composition of the human placenta. II. Lipid content. 665

MUNNELL, EQUINN W., AND TAYLOR, HOWARD C., JR. Complications and fetal mortality in 136 cases of multiple pregnancy, 588

MYERS, RICHARD T. (WITH LOCK, FRANK R.), Endometriosis in association with pregnancy, 556

N

NASH, FRANCIS J., Diabetes insipidus and pre-eclampsia, 863

NECHTOW, MITCHELL J. (WITH REICH, WALTER J.), Primary lipoma of uterus, 157

NELSON, EDWARD W. (WITH COLLINS, CONRAD G.), Phlebothrombosis and thrombophlebitis in gynecology and obstetrics, 946

—, AND MICHAELS, JACK P., Acute postpartum necrosis of the anterior hypophysis, 817

NICHOLLS, RICHARD B., Rupture of the posterior vagina during normal coitus, 500

— (WITH ANDREWS, C. J.), Recurrent placenta previa, 347 (Correspondence)

NORA, ERNEST, AND CARR, CLAIRE E., Umbilical accessory liver, 330

NOYES, ROBERT W., Sickle-cell anemia in pregnancy, 469

NUGENT, FRED B. (WITH SCHEFFEY, LEWIS C., AND LANG, WARREN R.), Clinical and pathologic aspects of primary sarcoma of the uterine tube, 904

NUZUM, THOMAS O. (WITH HAMMOND, HOWARD, JR.), Adult Mediterranean anemia complicated by pregnancy, 686

O

ODELL, LESTER D., AND PLASS, E. D., Intrapartum fever; a preliminary study, 89

P

PAGE, ERNEST W., The value of plasma pitocinase determinations in obstetrics, 1014

—, HUNT, MARJORIE, AND LUCIA, S. P., The antepartum prediction of hemolytic disease of the newborn, 794

PALMER, RUFUS E., III (WITH HEADINGS, DONALD M.), Relation of early rising to morbidity in cesarean section, 661

PARMLEY, RAY T., AND ADRIANI, JOHN, Saddle block anesthesia with nupercaine in obstetrics, 636

PAVEY, CHARLES W., Modification of the Ericson and Johnson resuscitator, 867

PENNELL, MELVIN T., AND KUKRAL, ALBERT J., An unusual case of holoacephalus, 669

PHILPOTT, N. W., LATOUR, J. P. A., AND VAN-DORSSER, G. J. E., Review of cases of Rh iso-immunization during the past five years in the Royal Victoria Montreal Maternity Hospital, 926

PLASS, E. D. (WITH ODELL, LESTER D.), Intrapartum fever; a preliminary study, 89

POMMERENKE, W. T., Cyclic changes in the physical and chemical properties of cervical mucus, 1023

POTTER, J. CRAIG, Winged stem pessary to correct stenosis of cervix, 164

PRATT, J. P., KAUCHER, MILDRED, MOYER, ELSIE, RICHARDS, ALLEN J., AND WILLIAMS, HAROLD H., Composition of the human placenta. II. Lipid content, 665

—, —, RICHARDS, ALLEN J., WILLIAMS, HAROLD H., AND MACY, ICIE G., Composition of the human placenta. I. Proximate composition, 402

—, RODERUCK, CHARLOTTE, CORYELL, MARGARET, AND MACY, ICIE G., Composition of the human placenta. III. Vitamin content, 783

PREECE, JOHN (WITH CHESLEY, LEON C., AND COSGROVE, S. A.), Hydatidiform mole, with special reference to recurrence and associated eclampsia, 311

PROSKAUER, GEORGE G., Solid teratomas of the ovary with neurological metastases, 845

R

RANDALL, J. H. (WITH KELBERG, MELVIN R.), Torsion of adnexal tumors and its relation to surgical emergency, 464

RANDALL, LAWRENCE M., Amenorrhea not associated with pregnancy in young women, 975

REICH, WALTER J., AND NECHTOW, MITCHELL J., Primary lipoma of uterus, 157

REID, DUNCAN E., The treatment of prolonged labor with posterior pituitary extract, 719

REIS, RALPH A., On the origin of certain perisalpingeal cysts, 964

REYNOLDS, VERNE J., Addition of penicillin sodium to anesthetic agent for local infiltration anesthesia, 641

RICHARDS, ALLEN J. (WITH PRATT, J. P., KAUCHER, MILDRED, MOYER, ELSIE, AND WILLIAMS, HAROLD H.), Composition of the human placenta. II. Lipid content, 665

— (WITH PRATT, J. P., KAUCHER, MILDRED, WILLIAMS, HAROLD H., AND MACY, ICIE G.), Composition of the human placenta. I. Proximate composition, 402

RIVETT, LOUIS CARNAC, Hydramnios (the Joseph Brettauer Memorial Lecture), 890

RODERUCK, CHARLOTTE (WITH PRATT, J. P., CORYELL, MARGARET, AND MACY, ICIE G.), Composition of the human placenta. III. Vitamin content, 783

ROSSMAN, I., AND BARTELMEZ, G. W., Delayed ovulation, a significant factor in the variability of the menstrual cycle, 28

ROUSUCK, A. ASHLEY (WITH TREUSCH, JEROME V., AND HUNT, ARTHUR B.), Infrequency of carcinoma of the uterine cervix among Jewish women, 162

RUCKER, M. PIERCE, Constriction ring dystocia, 984

S

SANES, S., AND KAMINSKI, CHESTER A., Spontaneous rupture of the liver in eclampsia with fatal hemoperitoneum, 325

SAVEL, LEWIS E., An aid in the diagnosis of fetal polarity, 861

SCADRON, SAMUEL J. (WITH WEINBERG, ARTHUR), The value and limitations of pelvioradiography in the management of dystocia, with special reference to midpelvic capacity, 255

SCHEFFEY, LEWIS C., LANG, WARREN R., AND NUGENT, FRED B., Clinical and pathologic aspects of primary sarcoma of the uterine tube, 904

—, THUDIUM, WILLIAM J., FARELL, DAVID M., AND HAHN, GEORGE A., Controversial factors in the management of fundal carcinoma, 529

SCHOENECK, FERDINAND J. (WITH BERNSTEIN, PHINEAS, AND ZERNER, HERBERT), Government sponsorship of a maternity program in wartime, 510

SCHUMANN, EDWARD A., The ways of doctors and the practice of physic (Presidential Address, American Gynecological Society), 881

SEWALL, C. WESLEY, AND COULTON, DONALD, Manual removal of the placenta; a benign procedure, 564

SHARKEY, JOHN A., AND HESS, CATHERINE B., The effect of essential hypertension on pregnancy, 672

SIEGLER, SAMUEL, A new method of treatment for vaginitis and cervicitis, 1

—, AND SILVERSTEIN, LOUIS M., Multiple primary carcinomas, 474

SILBERNAGEL, WYNNE M., AND BURT, OLAN P., Pyridoxine in nausea and vomiting of pregnancy, 173 (Correspondence)

SILVERSTEIN, LOUIS M. (WITH SIEGLER, SAMUEL L.), Multiple primary carcinomas, 474
SMITH, JOSEPH T., Simplified apparatus for insufflation of the tubes with carbon dioxide, 501
SOLOMON, ERNST M. (WITH LEVENTHAL, MICHAEL L.), Pelvic endometriosis as a cause of hydronephrosis, 692
SPATT, SAMUEL D., Adenomyosis of the uterus, 581
SPECK, GEORGE, Early diagnosis of anencephaly, 878 (Correspondence)
SPIVACK, MARY, The anatomic peculiarities of the human umbilical cord and their clinical significance, 387
STANDER, H. J. (WITH STROMME, W. B.), Retroperitoneal tumors simulating genital tract neoplasms, 456
—, BONSNES, R. W., AND STROMME, W. B., Late postpartum eclampsia, 765
STROMME, W. B. (WITH STANDER, H. J., AND BONSNES, R. W.), Late postpartum eclampsia, 765
—, AND KUDER, KATHERINE, Heart disease in pregnancy, 264
—, AND STANDER, H. J., Retroperitoneal tumors simulating genital tract neoplasms, 456
STUDDIFORD, W. E., Absorbable (oxidized) gauze as a hemostatic agent in gynecologic surgery, 495

T

TAYLOR, HOWARD C., JR. (WITH LANGMAN, LOUIS), The selection of forceps for midpelvic arrest of the vertex, 773
— (WITH MINNELL, EQUINN W.), Complications and fetal mortality in 136 cases of multiple pregnancy, 588
—, AND GUYER, HERBERT B., A seven-year history in early cervical cancer, 451
THELEN, CHRISTINE (WITH HESSELTINE, H. CLOSE), Sulfonamides as a prophylactic agent in conjunction with cesarean section, 813
THOMS, HERBERT, A discussion of pelvic variation and a report on the findings in 100 Negro women, 248
THORNHILL, PAIGE E., Gas bacillus infection primary in the newborn fetus, with report of a case spontaneously occurring at term, the mother surviving, 858
THUDIUM, WILLIAM J. (WITH SCHEFFEY, LEWIS C., FARELL, DAVID M., AND HAHN, GEORGE A.), Controversial factors in the management of fundal carcinoma, 529
TISDALL, LESLIE HUGHES, Present status of transfusion of whole blood and its derivatives in obstetrics and gynecology, 788
TREUSCH, JEROME V., HUNT, ARTHUR B., AND ROUSUCK, A. ASHLEY, Infrequency of carcinoma of the uterine cervix among Jewish women, 162
TURCOTTE, VINCENT J. (WITH DINDIA, ANTHONY H.), Extrauterine pregnancy, 321

U

ULLERY, JOHN C., Continuous spinal analgesia in cesarean section, 100

V

VANDORSSER, G. J. E. (WITH PHILPOTT, N. W., AND LATOUR, J. P. A.), Review of cases of Rh iso-immunization during the past five years in the Royal Victoria Montreal Maternity Hospital, 926
VEPROVSKY, EDWARD C. (WITH GOLDFARB, WILLIAM S.), Acute suppurative parotitis complicating pregnancy at term, 147

W

WAHRSINGER, PHILIP B. (WITH KUSHNER, J. IRVING), The Kielland forceps for use in the occipitoposterior and occipitotransverse positions, 110
WATERS, EDWARD G., A diagnostic technique for the detection of enterocele, 810
—, Mesenteric lymphangioma with intestinal obstruction complicating uterine carcinoma and fibromyoma, 478
— (WITH COSGROVE, S. A.), An evaluation of extraperitoneal cesarean section, 237
WATSON, B. P., AND GUSBERG, S. B., Prevention and treatment of carcinoma of the vulva, 179
WEINBERG, ARTHUR, AND SCADRON, SAMUEL J., The value and limitations of pelvioradiography in the management of dystocia, with special reference to midpelvic capacity, 255
WENGRAF, FRITZ, Psychoneurotic symptoms following hysterectomy, 645
WHITACRE, FRANK E. (WITH THE ASSISTANCE OF LOEB, WALTER M., JR., AND LOEB, LAURA), The time for postpartum sterilization, 1041
WILLIAMS, HAROLD H. (WITH PRATT, J. P., KAUCHER, MILDRED, MOYER, ELSIE, AND RICHARDS, ALLEN J.), Composition of the human placenta. II. Lipid content, 665
— (WITH PRATT, J. P., KAUCHER, MILDRED, RICHARDS, ALLEN J., AND MACY, ICIE G.), Composition of the human placenta. I. Proximate composition, 402
WILLSON, J. ROBERT, Veratrum viride in the treatment of the toxemias of pregnancy, 273
WINSON, S. G., An analysis of 257 cases of sterility, 631
WINTHER, NORA, Menorrheal problems in college women, 803

Y

YOUNG, RAYMOND L., Abnormal presentations among malformed infants, 419

Z

ZERNER, HERBERT (WITH BERNSTEIN, PHINEAS, AND SCHOENECK, FERDINAND J.), Government sponsorship of a maternity program in wartime, 510

SUBJECT INDEX*

A

Abdominal hysterectomy, total (Danforth), 218
Abortion and cervical dystocia, frequency of (Bret and Deplus), 872 (Abst.)
therapeutic, in a general hospital (Dannreuther), 54
Abstracts, 166, 340, 523, 695, 869
Adenomyosis of uterus (Spatt), 581
cystic (Gold and Kearns), 840
Adnexa, female, gonococcus in, persistence of (Cohn et al.), 83
Adnexal tumors, torsion of, and its relation to surgical emergency (Kelberg and Randall), 464
Adrenal-like tumor of ovary, origin of (Curtis), 115
Adrenals, diseases of (Soffer), 520 (B. rev.)
Amenorrhea not associated with pregnancy in young women (Randall), 975
American Board of Obstetrics and Gynecology, Inc., 175, 348, 528, 704, 880, 1054 (Items)
Gynecological Society, transactions of the sixty-ninth annual meeting, June 3-5, 1946, 881
Obstetrical and Gynecological Societies, roster of, 177, 705
Amniotic sac, diagnosis of rupture of (Colmeiro-Laforet), 873 (Abst.)
Analgesia, continuous spinal, in cesarean section (Ullery), 100
Ancylostomiasis and hypoproteinemia complicated by pregnancy (Aaberg), 854
Anemia, adult Mediterranean, complicated by pregnancy (Hammond and Nuzum), 686
of newborn, congenital, serum iron and serum bilirubin in (Vahlquist), 873 (Abst.)
Anencephaly during pregnancy, diagnosis of (Perez), 167 (Abst.)
early diagnosis of (Speck), 878 (Correspondence)
Anesthesia, continuous caudal, treatment of acute postpartum thrombophlebitis of the lower extremity by (Benson), 830
local infiltration, addition of penicillin sodium to anesthetic agent (Reynolds), 641
nupercaine in obstetrics, saddle block with (Parmley and Adriani), 636
obstetric, aspiration of stomach contents into the lungs during (Mendelson), 191
Antepartum prediction of hemolytic disease of newborn (Page et al.), 794
Antigalactogens (Gavioli), 526 (Abst.)
Arachnodactyly, unusual complication following skull injury (Schneider), 699 (Abst.)
Arrhenoblastoma, another case of (Curtis), 128
complicating pregnancy, case of (Brentnall), 700 (Abst.)
of ovary (Goldstine), 123
with report of two cases (Jones and Everett), 614
Artificial insemination (Mateos Fournier), 870 (Abst.)
Asphyxia in newborn, see-saw resuscitator for treatment of (Millen and Davies), 508
Aspiration of stomach contents into lungs during obstetric anesthesia (Mendelson), 191

B

Birth rate, declining, psychosomatic medicine and (Halliday), 869 (Abst.)
Blood, whole, and its derivatives, present status of transfusion of, in obstetrics and gynecology (Tisdall), 788
Books, review of new, 517
Breast, cancer of, some unusual aspects of (Daland), 695 (Abst.)
Breech delivery, fetal mortality in (Dieckmann), 349
risk in (Guyer and Heaton), 362
presentation at term, behaviour of fetus in utero with special reference to incidence of (Vartan), 702 (Abst.)
in the "concepcion palacios maternity" (Ascanio), 697 (Abst.)
Broad ligament, lipomas of, extending beyond the confines of the pelvis (Flickinger and Masson), 681

C

Cancer and malignancies, 526, 695 (Absts.)
cervical, a seven-year history in early (Taylor and Guyer), 451
of breast, some unusual aspects of (Daland), 695 (Abst.)
of cervix and pregnancy (Albertelli), 172 (Abst.); (Rojas), 171 (Abst.)
ovarian, review of one hundred cases of (Helsel), 435
Capillary filtration rates in pregnancy, further observations on (McLennan), 837
Carcinoma cervix uteri, treatment of, by radiotherapy (Sandler), 526 (Abst.)
corpus (Miller and Henderson), 894
fundal, management of, controversial factors in (Scheffey et al.), 529
of uterine cervix, infrequency of, among Jewish women (Treusch et al.), 162
of vulva, prevention and treatment of (Watson and Gusberg), 179
Carcinomas, multiple primary (Siegler and Silverstein), 474
Cardiospasm in the newborn (Vinson), 874 (Abst.)
Catheter, retention (Kennedy), 506
Cells and tissues, physical chemistry of (Höber et al.), 519 (B. rev.)
Cerebrovascular complications of pregnancy (Eller), 488
Cervical cancer, early, a seven-year history in (Taylor and Guyer), 451
mucus, cyclic changes in the physical and chemical properties of (Pommerenke), 1023
Cervicitis and vaginitis, new treatment for (Siegler), 1
Cervix, cancer of, and pregnancy (Albertelli), 172 (Abst.); (Rojas), 171 (Abst.)
chancroid of, report of two cases (Day), 171 (Abst.)
stenosis of, winged stem pessary to correct (Potter), 164
Cesarean operations on contaminated cases, intraperitoneal sulfonamide therapy in (Lopez Monti), 340 (Abst.)
section, 340 (Absts.)
continuous spinal analgesia in (Ullery), 100
extraperitoneal, evaluation of (Cosgrove and Waters), 237
relation of early rising to morbidity in (Headings and Palmer), 661
sulfonamides as a prophylactic agent in conjunction with (Hesseltine and Thelen), 813

*July, pp. 1-178; August, pp. 179-348; September, pp. 349-528; October, pp. 529-706; November, pp. 707-880; December, pp. 881-1066.

Chancroid of cervix, report of two cases (Day), 171 (Abst.)
Chemistry of cells and tissues, physical (Höber et al.), 519 (B. rev.)
Chorea and pregnancy (Gosende and Sandiano), 876 (Abst.)
Chorionepithelioma in an 18-year-old primigravida (Durburg), 484
spontaneous healing of, a case of probable (Recasens Mendez), 695 (Abst.)
Conception, ovulation and, in women, test for determining (Farris), 14
Constriction ring dystocia (Rucker), 984
Cornual resection, pathogenesis of pelvic infection as determined by, interpretation of (Falk), 66
Corpus carcinoma (Miller and Henderson), 894
Correspondence, anencephaly, early diagnosis of (Speck), 878
lactobacillus therapy in vaginitis due to trichomonas (Loeser), 879
pyridoxine in nausea and vomiting of pregnancy (Silbernagel and Burt), 173
recurrent placenta previa (Andrews and Nicholls), 347
the Guterman pregnancy test (Guterman), 174
traveling in pregnancy (Javert), 347
Cyclic changes in physical and chemical properties of cervical mucus (Pommerenke), 1023
Cyst, ovarian, a large (Hofmeister), 133
Cystadenoma of ovary, serous, bilateral concomitant fibroma and (Copland and Coleman), 141
Cystic adenomyosis of uterus (Gold and Kearns), 840
Cystoscope, air, with a universal handle and external light (Leff), 505
Cysts, perisalpingeal, origin of certain (Reis), 964

D

Delivery, breech, fetal mortality in (Dieckmann), 349
risk in (Guyer and Heaton), 362
Diabetes insipidus and pre-eclampsia (Nash), 863
Diaphragmatic hernia, congenital (Thompson and Blanc), 169 (Abst.)
Diet, high protein, low caloric, for prevention of toxemia of pregnancy (Luikart), 428
Doctors, the ways of, and the practice of physic (Schumann), 881
Dye poisoning in the nursery (Graubarth et al.), 699 (Abst.)
Dystocia, constriction ring (Rucker), 984
pelvioradiography in managemnet of, value and limitations of, with special reference to midpelvic cavity (Weinberg and Scadron), 255

E

Eclampsia, hydatidiform mole, with special reference to recurrence and associated (Chesley et al), 311
postpartum, late (Stander et al), 765
spontaneous rupture of liver in, with fatal hemoperitoneum (Sanes and Kaminski), 325
study on the newborn in (Orengo Diaz del Castillo), 345 (Abst.)
Eclamptic patients, future renal function of (Kunz and Raffo), 525 (Abst.)
Ectopic pregnancy, clinical evaluation of (Marchetti et al), 544
errors in diagnosis of (Clerc), 695 (Abst.)
interstitial (Delascio and Assali), 341 (Abst.)
radiologic aspects of (deMoracs), 342 (Abst.)
Electrical potentials of human uterus in labor (Dill and Maiden), 735
Embryology, contributions to (Carnegie Institution of Washington), 519 (B. rev.)
human (Patten), 518 (B. rev.)
Endocrinology, 340 (Absts.)
Endolymphatic stromal myosis (Henderson), 1000
Endometrioma interstitiale, so-called, with report of three possible cases (DeCarle), 523 (Abst.)
Endometriosis, conservative surgery in (Beecham), 707
in association with pregnancy (Lock and Myers), 556
pelvic, cause of hydronephrosis (Leventhal and Solomon), 692
Endometrium, tuberculosis of (Di Guglielmo and Pepe) 523 (Abst.)
Enterocele, diagnostic technique for detection of (Waters), 810
Enterouterine fistula (Hawkes), 150
Environment in obstetrics (Moore), 993
Episiotomy, technic to obtain anatomical cicatrization (Otero), 344 (Abst.)
Ericson and Johnson resuscitator, modification of (Pavey), 867
Erythroblastosis fetalis, association of, and accidental antepartum hemorrhage (Burch), 875 (Abst.)
clinical analysis (Leonard), 700 (Abst.)
in mothers with Rh positive blood (Polayes), 167 (Abst.)
Extraperitoneal cesarean section, evaluation of (Cosgrove and Waters), 237
Extrauterine pregnancy, 341, 695 (Absts.); (Dindia and Turcotte), 321

F

Fallopian tube, sliding hernia of (Gordon), 336
Fecundity, female, waking temperature in relation to (Barton and Wiesner), 869 (Abst.)
Fetal mortality in breech delivery (Dieckmann), 349
in 136 cases of multiple pregnancy, complications and (Munnell and Taylor), 588
polarity, aid in diagnosis of (Savel), 861
risk in breech delivery (Guyer and Heaton), 362
Fetus in utero, behaviour of, with special reference to incidence of breech presentation at term (Vartan), 702 (Abst.)
survival of, effect of prediabetic state on, and on the birth weight of the newborn infant (Miller), 700 (Abst.)
Fibroma, abdominal wall, simulating ovarian cystoma (McLennan and Holmstrom), 154
bilateral concomitant, and serous cystadenoma of ovary (Copland and Coleman), 141
Fistula, enterouterine (Hawkes), 150
Follicle ripening, studies on (Van Ravensteyn), 518 (B. rev.)
Forceps, selection of, for midpelvic arrest of vertex (Langman and Taylor), 773
Fundal carcinoma, management of, controversial factors in (Scheffey et al), 529

G

Gas bacillus infection in unborn fetus occurring at term, mother surviving (Thornhill), 858
Gauze, absorbable (oxidized) as a hemostatic agent in gynecologic surgery (Studdiford), 495
Genital bleeding two or more years after spontaneous cessation of menstruation, pathologic findings in (Cheek and Davis), 756
hypoplasia, social factors in (Rodriguez de Ginocchio), 345 (Abst.)
prolapse, recurrence of (Mazza), 342 (Abst.)
tract neoplasms, retroperitoneal tumors simulating (Stromme and Stander), 456

Genital—Cont'd
tuberculosis, female, significance, diagnosis and treatment (Kovacs), 870 (Abst.)
Goiter, prevention of, in newborn (Wespi), 699 (Abst.)
prophylaxis with iodized salt, reduction of deafness and dumbness in Switzerland as result of (Wespi), 699 (Abst.)
Gonococcal pelvic inflammatory disease in female, acute, treatment of, with penicillin (Gray), 171 (Abst.)
Gonococcus in female adnexa, persistence of (Cohn et al), 83
Granulosa-cell tumor of ovary (Bianco and Favorite), 677; (Hodgson et al), 870 (Abst.)
Guterman pregnancy test (Guterman), 174 (Correspondence)
Gynatresia, postpartum traumatic (B'rd), 704 (Abst.)
Gynecologic disorders, influence of, on urinary system (Hundley and Diehl), 696 (Abst.)
nursing (Crossen and Hoffert), 517 (B. rev).
operations, 343 (Abs's.)
patients, thrombophlebitis and phlebothrombosis in (Meigs and Ingersoll), 938
practice, psychosomatic approach in (Bryson), 871 (Abst.)
surgery, absorbable (oxidized) gauze as a hemostatic agent in (Studdiford), 495
surgical procedures, critical study of 390 major (Malone), 291
Gynecology, 342, 523, 696, 870 (Absts.)
in industry (Peters and Foster), 698 (Abst.)
phlebothrombosis and thrombophlebitis in (Collins and Nelson), 946
synopsis of (Crossen), 517 (B. rev.)
urology in (Ercole), 342 (Abst.)

H

Heart disease in pregnancy (Stromme and Kuder), 264
Hemolytic disease associated with Rh factor in twin pregnancies (Conti and Glenn), 446
of newborn (Leonard), 700 (Abst.)
antepartum prediction of (Page et al), 794
Hemoperitoneum, fatal, spontaneous rupture of liver in eclampsia with (Sanes and Kaminski), 325
Hemorrhage, massive, rupture of uterus with, an unusual case of (Douglas), 135
Hernia, congenital diaphragmatic (Thompson and Blanc), 169 (Abst.)
sliding, of Fallopian tube (Gordon), 336
Holoacephalus, an unusual case of (Pennell and Kukral), 669
Hydatidiform mole, with special reference to recurrence and associated eclampsia (Chesley et al), 311
Hydramnios (Rivett), 890
successful treatment of, with ammonium chloride (Abrams and Abrams), 299
Hydronephrosis, pelvic endometriosis as cause of (Leventhal and Solomon), 692
Hypernephroma of ovary, origin of (Curtis), 115
Hypertension, essential, an introduction to (Herndon), 521 (B. rev.)
effect of, on pregnancy (Sharkey and Hess), 672
in pregnancy (Monckeberg), 876 (Abst.)
Hyperthyroidism in women and in pregnancy (Perez), 340 (Abst.)
Hypnoanalysis, treatment of psychogynecic disorders by (Kroger), 409
Hypophysis, anterior, acute postpartum necrosis of (Nelson and Michaels), 817
Hypoproteinemia, ancylostomiasis and, complicated by pregnancy (Aaberg), 854
Hysterectomies, vaginal, report on 2,798 (Campbell), 598
study of 500 (Falk and Bunkin), 623
Hysterectomy, psychoneurotic symptoms following (Wengraf), 645
Hysterectomy—Cont'd
total abdominal (Danforth), 206
and the "occasional operator," (Gaston), 343 (Abst.)

I

Icterus gravis neonatorum (Vahlquist), 873 (Abst.)
Ileal atresia, congenital, with gangrene, perforation and peritonitis in newborn infant (Arnheim), 345 (Abst.)
Impetigo neonatorum, penicillin ointment in treatment of (Kendig and Fiske), 874 (Abst.)
Infants, malformed, abnormal presentations among (Young), 419
Infection, pelvic, pathogenesis of, as determined by cornual resection, interpretation of (Falk), 66
Insemination, artificial (Mateos Fournier), 870 (Abst.)
International Congress of Obstetrics and Gynecology, 1054 (Item)
Intrapartum fever, a preliminary study (Odell and Plass), 89
Iron metabolism during pregnancy (Renaer), 518 (B. rev.)
Item, American Board of Obstetrics and Gynecology, Inc., 175, 348, 528, 704, 880, 1054
The International Congress of Obstetrics and Gynecology, 1054
Third American Congress on Obstetrics and Gynecology, 880

K

Kielland forceps for use in occipitoposterior and occipitotransverse positions (Kushner and Wahrsinger), 110

L

Labor, conduct of, in presence of thrombosis (Pali), 698 (Abst.)
fourth stage of (Greenberg), 746
in overweight women (Biro), 697 (Abst.)
induction of, different methods of (Chanal), 873 (Abst.)
medical (Morassi), 344 (Abst.)
management, complications, 343, 697, 872 (Absts.)
medical induction of (Morassi), 344 (Abst.)
prolonged, treatment of, with posterior pituitary extract (Reid), 719
uterus in, electrical potentials of human (Dill and Maiden), 735
Lactobacillus therapy in vaginitis due to trichomonas (Loeser), 879
Leech treatment in obstetrics and gynecology (Kese), 697 (Abst.)
Leiomyosarcoma of uterus with metastasis (Brooke and Thomason), 695 (Abst.)
Lipomas of broad ligament extending beyond the confines of pelvis (Flickinger and Masson), 681
of uterus, primary (Reich and Nechtow), 157
Liver, spontaneous rupture of, in eclampsia with fatal hemoperitoneum (Sanes and Kaminski), 325
umbilical accessory (Nora and Carr), 330
Luteinoma, origin of (Curtis), 115
Luteoma, origin of (Curtis), 115
Lymphangioma, mesenteric, with intestinal obstruction complicating uterine carcinoma and fibromyoma (Waters), 478

M

Malformed infants, abnormal presentations among (Young), 419
Malignancies, 171 (Absts.)
Manchester operation, with special reference to parturition and complete prolapse (Gordon), 228

Masculinovoblastoma, origin of (Curtis), 115
Maternal mortality in province of Buenos Aires (Leon), 525 (Abst.)
obstetric paralysis (Cole), 372
weight gain, relationship of, to weight of newborn infant (Klein), 574
Maternity program in wartime, government sponsorship of (Bernstein et al), 510
Medical care of young women, clinical significance of data accumulated in (Hardy), 872 (Abst.)
Medicine, preventive, and public health (Smillie), 521 (B. rev.)
Mediterranean anemia, adult, complicated by pregnancy (Hammond and Nuzum), 686
Menorrheal problems in college women (Winther), 803
Menstrual cycle, variability of, delayed ovulation a significant factor in (Rossman and Bartelmez), 28
Menstruation, spontaneous cessation of, pathologic findings in genital bleeding two or more years after (Cheek and Davis), 756
Mesenteric lymphangioma with intestinal obstruction complicating uterine carcinoma and fibromyoma (Waters), 478
Micturition, muscle of (Kennedy), 206
Multiple pregnancy, complications and fetal mortality in 136 cases of (Munnell and Taylor), 588
Muscle of micturition (Kennedy), 206

N

Necrology, Eden, Thomas Watts, 877
McGlinn, John A., 1054
Ryder, George Hope, 527
Newborn, 345, 699, 873, (Absts.)
asphyxia in, see-saw resuscitator for treatment of (Millen and Davies), 508
cardiospasm in (Vinson), 874 (Abst.)
congenital anemia of, serum iron and serum bilirubin in (Vahlquist), 873 (Abst.)
hemolytic disease of (Leonard), 700 (Abst.)
antepartum prediction of (Page et al), 794
in eclampsia, studies on (Orengo Diaz del Castillo), 345 (Abst.)
infant, congenital ileal atresia with gangrene, perforation, and peritonitis in (Arnheim), 345 (Abst.)
hereditary skin defect in (Freud et al), 874 (Abst.)
weight of, relationship of maternal weight gain to (Klein), 574
oronasal cavity of, bacteriology of (Cornelison et al), 797
prevention of goiter in (Wespi), 699 (Abst.)
Nupercaine in obstetrics, saddle block anesthesia with (Parmley and Adriani), 636
Nursery, dye poisoning in (Graubarth et al), 699 (Abst.)
Nutrition in pregnancy (Lund), 166 (Abst.)

O

Obstetric anesthesia, aspiration of stomach contents into lungs during (Mendelson), 191
paralysis, maternal (Cole), 372
patient, overweight (Odell and Mengert), 166 (Abst.)
Obstetrics and gynecology, leech treatment in (Kese), 697 (Abst.)
synopsis of (Bourne), 517 (B. rev.)
transfusion of whole blood and its derivatives in, present status of (Tisdall), 788
yearbook of, 1945 (Greenhill), 517 (B. rev.)
environment in (Moore), 993
nupercaine in, saddle block anesthesia with (Parmley and Adriani), 636
operative, preventive local chemotherapy in (Perez and Blanchard), 703 (Abst.)
Obstetrics—Cont'd
phlebothrombosis and thrombophlebitis in (Collins and Nelson), 946
plasma pitocinase determinations in, value of (Page), 1014
practical (Barbosa), 518 (B. rev.)
Rh factor in (Belson), 106
some clinical aspects of (King and Davenport), 917
Occipitoposterior and occipitotransverse positions, Kielland forceps for use in (Kushner and Wahrsinger), 110
Ophthalmia neonatorum, penicillin locally in eyes of newborn infants to prevent (Bloxsom), 874 (Abst.)
Oronasal cavity of newborn, bacteriology of (Cornelison et al), 797
Ovarian cancer, review of one hundred cases of (Helsel), 435
cyst, diagnosis of, new procedure for (Abad Colomer), 342 (Abst.)
large (Hofmeister), 133
cystoma, abdominal wall fibroma simulating (McLennan and Holmstrom), 154
Ovaries, condition of, in cases of uterine myoma (Calvo Marcos and Botella Llusia), 342 (Abst.)
Ovary, adrenal-like tumor of, origin of (Curtis), 115
arrhenoblastoma of (Goldstine), 123
with a report of two cases (Jones and Everett), 614
cystadenoma of, serous, bilateral concomitant fibroma and (Copland and Coleman), 141
granulosa- and theca-cell tumors of, question of so-called (Scheidegger), 697 (Abst.)
granulosa-cell tumor of (Bianco and Favorite), 677; (Hodgson et al), 870 (Abst.)
multilocular pseudomucinous cystadenoma of, Meigs' syndrome in a case of (Millet and Shell), 523 (Abst.)
solid teratomas of, with neurological metastases (Proskauer), 845
Overweight obstetric patient (Odell and Mengert), 166 (Abst.)
women, labor in (Biro), 697 (Abst.)
Ovulation and conception in women, test for determining (Farris), 14
basal body temperature grasps as an index to (Tompkins), 699 (Abst.)
delayed, a significant factor in the variability of the menstrual cycle (Rossman and Bartelmez), 28
Ovum, intact dead, retained, treatment of (Turenne), 346 (Abst.)

P

Parotitis, acute suppurative, complicating pregnancy at term (Goldfarb and Veprovsky), 147
Parturition and complete prolapse, Manchester operation with special reference to (Gordon), 228
Pediatrics, textbook of (Nelson), 522 (B. rev.)
Pelvic infection, pathogenesis of, as determined by cornual resection, interpretation of (Falk), 66
masses, suppurative, rupture of (Miller), 871 (Abst.)
puerperal suppuration spontaneously opened into the rectum (Trivelli and Garcia), 168 (Abst.)
size, relative, graphic portrayal of (Mengert and Eller), 1032
variation, discussion of, and a report on the findings in 100 Negro women (Thoms), 248
Pelvioradiography in management of dystocia, value and limitations of, with special reference to midpelvic capacity (Weinberg and Scadron), 255
Penicillin locally in eyes of newborn infants to prevent ophthalmia neonatorum (Bloxsom), 874 (Abst.)

Penicillin—Cont'd
ointment in treatment of impetigo neonatorum (Kendig and Fiske), 874 (Abst.)
one-dose treatment of chronic gonorrheal vaginitis in children (Sako et al), 170 (Abst.)
puerperal infection treated with, two cases of grave (Keymer), 169 (Abst.)
pyopneumothorax in premature baby successfully treated with (Harris and Platou), 874 (Abst.)
sodium, addition of, to anesthetic agent for local infiltration anesthesia (Reynolds), 641
treatment of acute gonococcal pelvic inflammatory disease in female (Gray), 171 (Abst.)
Periarteritis nodosa occurring in first month of life, two cases of (Wilmer), 873 (Abst.)
Perisalpingeal cysts, origin of certain (Reis), 964
Pessary, winged stem, to correct stenosis of cervix (Potter), 164
Phlebothrombosis and thrombophlebitis in gynecologic patients (Meigs and Ingersoll), 938
in gynecology and obstetrics (Collins and Nelson), 946
Phlegmasia, postpartum, without fever or permanent tachycardia (Vignes), 168 (Abst.)
Physiology, synopsis of (Main), 521 (B. rev.)
Placenta attached to spleen, abdominal pregnancy with (Kushner and Dobrzynski), 160
human, composition of (Pratt et al), 402, 665, 783
lipid content (Pratt et al), 665
vitamin content (Pratt et al), 783
manual extraction of, and hydraulic injection (Dominguez Sisco and Aguero), 698 (Abst.)
removal (Sewall and Coulton), 564
previa, recurrent (Andrews and Nicholls), 347 (Correspondence)
study of 174 cases (Macafee), 701 (Abst.)
Placental thromboplastin, human, studies on (Copley), 344 (Abst.)
Plasma pitocinase determinations in obstetrics, value of (Page), 1014
Poliomyelitis in pregnancy (Fox and Sennet), 167 (Abst.)
Postpartum eclampsia, late, (Stander et al), 765
necrosis of anterior hypophysis, acute (Nelson and Michaels), 817
phlegmasia without fever or permanent tachycardia (Vignes), 168 (Abst.)
sterilization, time for (Whitacre et al), 1041
thrombophlebitis of lower extremity, acute, treatment of, by continuous caudal anesthesia (Benson), 830
uterus, physiology and clinical aspects of, during the first postplacental hour (Greenberg), 746
Pre-eclampsia, diabetes insipidus and (Nash), 863
Pregnancies, twin, hemolytic disease associated with the Rh factor in (Conti and Glenn), 446
Pregnancy, abdominal, with placenta attached to the spleen (Kushner and Dobrzynski), 160
acute salpingitis and (Bidoire), 346 (Abst.)
suppurative parotitis complicating pregnancy at term (Goldfarb and Veprovsky), 147
adult Mediterranean anemia complicated by (Hammond and Nuzum), 686
amenorrhea not associated with, in young women (Randall), 975
ancylostomiasis and hypoproteinemia complicated by (Aaberg), 854
and labor, rupture of uterus during, fifty cases of (Frid), 343 (Abst.)
anemia in, sickle-cell (Noyes), 469
Pregnancy—Cont'd
anencephaly during, diagnosis of (Perez), 167 (Abst.)
arrhenoblastoma complicating, case of (Brentnall), 700 (Abst.)
cancer of cervix and (Albertelli), 172 (Abst.); (Rojas), 171 (Abst.)
capillary filtration rates in, further observations on (McLennan), 837
carcinoma of the colon producing acute intestinal obstruction during (Finn and Lord), 524 (Abst.)
cerebrovascular complications of (Eller), 488
chorea and (Gosende and Sandiano), 876 (Abst.)
complications, 167, 346, 524, 700, 875 (Absts.)
early, clinical sign diagnostic of (Braga), 702 (Abst.)
syphilis complicated by, treatment with massive arsenotherapy (Curtis and Morrow), 284
ectopic, clinical evaluation of (Marchetti), 544
errors in diagnosis of (Clerc), 695 (Abst.)
radiologic aspects of (deMoracs), 342 (Abst.)
effect of essential hypertension on (Sharkey and Hess), 672
electrophoretic analysis of serum in, and in pregnancy toxemia (Lagercrantz), 876 (Abst.)
endometriosis in association with (Lock and Myers), 556
extrauterine, 341, 695 (Absts.); (Dindia and Turcotte), 321
Guterman test (Guterman), 174 (Correspondence)
heart disease and (Stromme and Kuder), 264
histaminase activity during, short study of (Koloszynski), 877 (Abst.)
hypertension in (Monckeberg), 876 (Abst.)
hyperthyroidism in women and in (Perez), 340 (Abst.)
interstitial ectopic (Delascio and Assali), 341 (Abst.)
excision of cornu because of, pregnancy and rupture in scar area after salpingectomy with (Kaeser), 696 (Abst.)
iron metabolism during (Renaer), 518 (B. rev.)
maternal rubella in early weeks of, congenital anomalies following (Albaugh), 874 (Abst.)
multiple, complications and fetal mortality in 136 cases of (Munnell and Taylor), 588
with early abortion of one fetus (Butler and Howard), 163
nausea and vomiting of, pyridoxine in (Silbernagel and Burt), 173 (Correspondence)
nutrition in (Lund), 166 (Abst.)
pernicious vomiting of, due to sensitivity to semen (James), 701 (Abst.)
pertussis vaccine during, immunity response of mothers and babies to injections of (Kendrick et al), 702 (Abst.)
physiology, diagnosis, 166, 702, 877 (Absts.)
poliomyelitis in (Fox and Sennet), 167 (Abst.)
prolonged (Schwarcz and Pinto), 524 (Abst.)
Rh factor in, some observations upon (Ingram), 440
rubella during, its sequelae of congenital defects in the child (Gregg), 167 (Abst.)
sickle-cell anemia in (Noyes), 469
thiouracil in, effect on fetal thyroid (Davis and Forbes), 876 (Abst.)
toxemia of, endocrine factors in mechanism of (Hofbauer), 525 (Abst.)
high protein, low caloric diet for prevention of (Luikart), 428
toxemias of, veratrum viride in treatment of (Willson), 273

Pregnancy—Cont'd
traveling in (Javert), 347 (Correspondence)
tubal, bilateral simultaneous (Harris and Leviton), 492; (MacDonald and Masters), 850
simultaneous ruptured, and intrauterine pregnancy with subsequent delivery of a normal infant (Howard), 696 (Abst.)
weight control, diet, and fluid balance in (Loughran), 42
Pregnant uterus, five months', instrumental rupture of (Badia), 167 (Abst.)
Prenatal tuberculosis (Elizalde and Latienda), 345 (Abst.)
Presentations, abnormal, among malformed infants (Young), 419
Prolapse of umbilical cord (Gusberg), 826
Psychogynecic disorders, treatment of, by hypnoanalysis (Kroeger), 409
Psychoneurotic symptoms following hysterectomy (Wengraf), 645
Psychosomatic approach in gynecologic practice (Bryson), 871 (Abst.)
medicine and the declining birth-rate (Halliday), 869 (Abst.)
Puerperal infection treated with penicillin, two cases of grave (Keymer), 169 (Abst.)
rising, early (King), 657
Puerperium, 168, 526, 703 (Absts.)
late bleeding in, cause of (Palik and Rechwitz), 703 (Abst.)
spontaneous expulsion of intraparietal uterine tumors during (Rodriguez), 703 (Abst.)
Pyelonephritis associated with puerperal state, bacteriologic study of (Trillat and Notter), 169 (Abst.)
Pyopneumothorax in premature baby successfully treated with penicillin (Harris and Platou), 874 (Abst.)
Pyosalpinx evacuated spontaneously through uterine ostium of the tube (De la Colina and Dixon), 526 (Abst.)
Pyridoxine in nausea and vomiting of pregnancy (Silbernagel and Burt), 173 (Correspondence)

R

Radiotherapy, treatment of carcinoma cervix uteri by (Sandler), 526 (Abst.)
Renal function of eclamptic patients, the future (Kunz and Raffo), 525 (Abst.)
Respiration during the first hour of life (Gottschalk), 651
Resuscitator, Ericson and Johnson, modification of (Pavey), 867
see-saw, for treatment of asphyxia in newborn (Millen and Davies), 508
Retention catheter (Kennedy), 506
Retroperitoneal tumors simulating genital tract neoplasms (Stromme and Stander), 456
Rh factor, hemolytic disease associated with, in twin pregnancies (Conti and Glenn), 446
in obstetrics (Belson), 106
some clinical aspects of (King and Davenport), 917
in pregnancy, some observations upon (Ingram), 440
Rh iso-immunization, review of cases, during past five years in the Royal Victoria Montreal Maternity Hospital (Philpott et al), 926
Roster of American Obstetrical and Gynecological Societies, 177, 705
Rupture of suppurative pelvic masses (Miller), 871 (Abst.)
Ruptured uteri, an analytical report (Beacham and Varino), 701 (Abst.)

S

Salpingectomy, pregnancy and rupture in scar area after, with excision of cornu because of interstitial pregnancy (Kaeser), 696 (Abst.)
Salpingitis, acute, and pregnancy (Bidoire), 346 (Abst.)
Sarcoma of uterine tube, primary, clinical and pathologic aspects of (Scheffey et al), 904
of vagina (Diehl and Haught), 302
Semen analysis in 1,500 cases of sterile marriage (MacLeod and Hotchkiss), 34
Sex hormones, biological action of (Burrows), 520 (B. rev.)
Sickle-cell anemia in pregnancy (Noyes), 469
Spinal analgesia, continuous, in cesarean section (Ullery), 100
Stenosis of cervix, winged stem pessary to correct (Potter), 164
Sterile marriage, semen analysis in 1,500 cases of (MacLeod and Hotchkiss), 34
Sterility, analysis of 257 cases (Winson), 631
fertility, contraception, 869 (Absts.)
Sterilization, postpartum, time for (Whitacre et al), 1041
Stomach contents, aspiration of, into lungs during obstetric anesthesia (Mendelson), 191
Strassmann's operation in some uterine malformations (Borras), 343 (Abst.)
Streptococci isolated from female urinary tract, significance of (Schaub and Davis), 872 (Abst.)
Sulfonamide therapy, intraperitoneal, in cesarean operations on contaminated cases (Lopez Monti), 340 (Abst.)
of vulvar condylomatosis, trial of (Carceller), 170 (Abst.)
Sulfonamides as a prophylactic agent in conjunction with cesarean section (Hesseltine and Thelen), 813
Surgery, conservative, in endometriosis (Beecham), 707
gynecologic, absorbable (oxidized) gauze as a hemostatic agent in (Studdiford), 495
Syphilis, early, complicated by pregnancy, treatment with massive arsenotherapy (Curtis and Morrow), 284

T

Teratomas, solid, of ovary with neurological metastases (Proskauer), 845
Therapy, Cornell conferences on (Gold et al), 521 (B. rev.)
Thiouracil in pregnancy, effect on fetal thyroid (Davis and Forbes), 876 (Abst.)
Third American Congress on Obstetrics and Gynecology, 880 (Item)
Thrombophlebitis, acute postpartum, of lower extremity, treatment of, by continuous caudal anesthesia (Benson), 830
and phlebothrombosis in gynecologic patients (Meigs and Ingersoll), 928
in gynecology and obstetrics (Collins and Nelson), 946
Thromboplastin, human placental, studies on (Copley), 344 (Abst.)
Thrombosis, conduct of labor in presence of (Pali), 698 (Abst.)
Torsion of adnexal tumors and its relation to surgical emergency (Kelberg and Randall), 464
Toxemia of pregnancy, electrophoretic analysis of serum in (Langercrantz), 876 (Abst.)
endocrine factors in mechanism of (Hofbauer), 525 (Abst.)
high protein, low caloric diet for prevention of (Luikart), 428
veratrum viride in treatment of (Willson), 273
Tubal peristalsis, question of (Müller), 696 (Abst.)
pregnancy, bilateral simultaneous (Harris and Leviton), 492; (MacDonald and Masters), 850
simultaneous ruptured, and intrauterine pregnancy with subsequent delivery of a normal infant (Howard), 696 (Abst.)

Tube, uterine ostium of pyosalpinx evacuated spontaneously through (De la Colina and Dixon), 526 (Abst.)
Tuberculosis, genital, significance, diagnosis, and treatment (Kovacs), 870 (Abst.)
of endometrium (Di Guglielmo and Pepe), 523 (Abst.)
prenatal (Elizalde and Latienda), 345 (Abst.)
Tubes, insufflation of, with carbon dioxide, simplified apparatus for (Smith), 501
Tumor, adrenal-like, of ovary, origin of (Curtis), 115
granulosa-cell of ovary (Bianco and Favorite), 677; (Hodgson et al), 870 (Abst.)
intraparietal uterine, spontaneous expulsion of, during the puerperium (Rodriguez), 703 (Abst.)
Tumors, adnexal, torsion of, and its relation to surgical emergency (Kelberg and Randall), 464
granulosa- and theca-cell, of ovary, question of co-called (Scheidegger), 697 (Abst.)
retroperitoneal, simulating genital tract neoplasms (Stromme and Stander), 456
Twin pregnancies, hemolytic disease associated with Rh factor in (Conti and Glenn), 446

U

Umbilical accessory liver (Nora and Carr), 330
cord, human, anatomic peculiarities of, and their clinical significance (Spivack), 387
prolapse of (Gusberg), 826
Urinary system, influence of gynecologic disorders on (Hundley and Diehl), 696 (Abst.)
tract, female, streptococci isolated from, significance of (Schaub and Davis), 872 (Abst.)
Urology in gynecology (Ercole), 342 (Abst.)
Uteri, retroverted, combined procedure for anteroversion of (Javert), 865
ruptured, an analytical report (Beacham and Varino), 701 (Abst.)
Uterine carcinoma and fibromyoma, mesenteric lymphangioma with intestinal obstruction complicating (Waters), 478
cervix, carcinoma of, infrequency of, among Jewish women (Treusch et al), 162
contraction rings, varying degrees of, clinical diagnosis of (Johnson), 74
malformations, Strassmann's operation in some (Borras), 343 (Abst.)
myoma, condition of ovaries in cases of (Calvo Marcos and Botella Llusia), 342 (Abst.)
tube, sarcoma of, clinical and pathologic aspects of primary (Scheffey et al), 904
Uterine—Cont'd
x-ray therapy, obstetrical consequences of (Bret and Deplus), 872 (Abst.)
Uterus, adenomyosis of (Spatt), 581
cystic adenomyosis of (Gold and Kearns), 840
in labor, human, electrical potentials of (Dill and Maiden), 735
leiomyosarcoma of, with metastasis (Brooke and Thomason), 695 (Abst.)
lipoma of, primary (Reich and Nechtow), 157
postpartum, physiology and clinical aspects of, during first postplacental hour (Greenberg), 746
pregnant, instrumental rupture of a five months' (Badia), 167 (Abst.)
rupture of, during pregnancy and labor, fifty cases of (Frid), 343 (Abst.)
with massive hemorrhage, an unusual case of (Douglas), 135

V

Vagina, rupture of posterior, during normal coitus (Nicholls), 500
sarcoma of (Diehl and Haught), 302
Vaginal infections, 170 (Absts.)
hysterectomies, report on 2,798 (Campbell), 598
study of 500 (Falk and Bunkin), 623
Vaginitis and cervicitis, new method of treatment (Siegler), 1
and vulvar irritations in infants and children, current concepts of (Schauffler and Schauffler), 170 (Abst.)
chronic gonorrheal, in children, one-dose penicillin treatment of (Sako et al), 170 (Abst.)
due to trichomonas, lactobacillus therapy in (Loeser), 879 (Correspondence)
Venereal diseases, 171 (Absts.)
Veratrum viride in treatment of toxemias of pregnancy (Willson), 273
Vertex, midpelvic arrest of, selection of forceps for (Langman and Taylor), 773
Vitamin content of human placenta (Pratt et al), 783
Vomiting of pregnancy, pernicious, due to sensitivity to semen (James), 701 (Abst.)
Vulva, carcinoma of, prevention and treatment of (Watson and Gusberg) 179
Vulvar condylomatosis, sulfonamide therapy in a case of (Carceller), 170 (Abst.)

W

Weight control, diet, and fluid balance in pregnancy (Loughran), 42
curve, normal, of newly born, study of deviations from (De La Villa and Nieto), 875 (Abst.)
gain, maternal, relationship of, to weight of newborn infant (Klein), 574